Journal Homepage: - www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI:10.21474/IJAR01/2795
DOI URL: http://dx.doi.org/10.21474/IJAR01/2795
ISSN NO. 2320-5407

RESEARCH ARTICLE

A UNIQUE CO-RELATION: POSTMENOPAUSAL ESTROGEN DEFICIENCY AND ANEURYSMAL SUBARACHNOID HEMORRHAGE.

Dr. Malavika J. C. MS, DNBOBG[1] and Dr. Vijaykumar S. Shabadi M.Ch Neurosurgery[2].
1. Assistant Professor, S. S. Institute of Medical Sciences and Research Centre,Davangere, Karnataka, India.
2. Consultant Neurosurgeon,Dhanush Hospital and Research Centre, Bagalkot, Karnataka, India.

Manuscript Info

Manuscript History

Received: 15 November 2016
Final Accepted: 17 December 2016
Published: January 2017

Key words:-
Estrogen deficiency, aneurysm, sub-arachnoid haemorrhage, estrogen receptors, hormone replacement therapy.

Abstract

Background: Rupture of aneurysms often present as subarachnoid haemorrhage (SAH). It is one of the most severe form of stroke especially in female population. Estrogen has a potential influence on the vascular pathophysiology. Several reports have come up with the hypothesis of establishing the role of estrogen on SAH. Hence, revisiting the hypothesis of the possible relationship of estrogen with SAH is utmost necessary to find a rationale therapeutics based on understanding of pathophysiology.

Conclusion: Estrogen deficiency has significant impact on SAH. A practical approachbased on pathophysiology is vital in preventing this dreaded complication in peri-menopausal women harbouring unruptured aneurysms.

Introduction:-

Rupture of intracranial aneurysms often results in subarachnoid haemorrhage which is a dangerous variety of stroke. 50% of cases often succumb and another 20% are often left with debilitating disability. Of the 30% cases who survive, 10% lose life due to delay in treatment.[1,3,5] SAH has higher incidence in females compared to males and so is the mortality rate associated with it. There is also higher incidence of multiple aneurysms in female population compared to male population. Several meta-analysis and systematic reviews have postulated that in younger ages the incidence is higher in male population and after 50 years the incidence steadily increases in female population[2,6]. And also, cerebral aneurysms are found to occur more commonly in women who achieve early menopause substantiating the role of estrogen as a protective factor against growth of aneurysms[9]. Here is a need for an insight into this hypothesis and its possible therapeutic implications.

Aneurysms:-

Abnormal dilatations in the vessel wall are termed as aneurysms. Morphologically there are 2 major types of aneurysms:saccular and fusiform. Saccular aneurysms are more common in cerebral vasculature. They are thin walled spherical expansion from the branching regions of the major cerebral arteries. Fusiform aneurysms are more oblongated dilatations of the vessels and are often secondary to certain etiologies like atherosclerosis, dissections etc. SAH is more often associated with saccular aneurysms than fusiform aneurysms and been discussed in this context[11,15,17].

Corresponding Author:-Dr.Malavika J.C. MS, DNB OBG
Address:-Assistant Professor, S. S. Institute of Medical Sciences and Research Centre, Davangere, Karnataka, India.

The layers of cerebral vasculature wall are from within outside: tunica intima, tunica media and tunica adventitia. Internal elastic lamina separates intima from media and is composed of elastin. Tunica media is mainly composed of smooth muscle cells and collagen fibrils. Tunica adventitia mainly consists of vasa-vasorum, fibroblasts, elastin and collagen fibres. Collagen fibres are mainly produced by fibroblasts.Fibrobalsts are also responsible for repair and maintenance of connective tissue. It is the defect or loss of segments of tunica media that incites aneurysms. The production and degradation of collagen fibres is dependent on stretch of the wall of the vessels. The hemodynamic factors like shear stress and blood pressure play a vital role in the growth of aneurysms[11,12].

The 3 important determinants of aneurysms are : hypertension, increased vessel fragility and hemodynamic shearing stress. And interestingly estrogen can affect all these factors and thereby increase the risk of cerebral aneurysm formation. Low doseestrogen reduces blood pressure and so is the hormone replacement therapy. It also has conducive effect on lipid profiles which directly contributes to reduced risk for atherogenesisand plaque formation which weaken the vessel walls. The tunica media is composed of collagen type 1 and 3 which is the main structural matrix of major arteries including internal carotid arteries[14]. During post-menopause, connective tissues of the internal carotid arteries undergo degeneration contributing to aneurysm formation. Low dose estrogen and hormone replacement therapy promote strengthening of the connective tissue by promoting the formation of collagen 1 and 3 by fibroblasts and thereby preventing aneurysm formation and growth. Hence estrogen plays an important role in vascular and aneurysmal integrity through the control of collagen production and maturation in the vessel wall[17,18].

Estrogens:-

Endogenous estrogens include: estrone(E1), estradiol (E2) and estriol (E3). Majority of estrogens are formed in the liver or in peripheral tissues from androstenedione. Major circulating form is estradiol(E2) which is formed mainly in ovaries. The source and plasma levels vary with age. In post-menopausal women, estrone(E1),testosterone and circulating androstenedione are the major precursors of estrogen production in peripheral tissues. E2 metabolism also depends on genetic background, ethnicity, menopausal status and the phase of menstrual cycle. This variation in metabolism has immense effect on vascular integrity[11,18,19]. Estrogen receptors have very high affinity and specificity to circulating estrogens. There are sex and age related differences in the expression of these estrogen receptors. However ,estrogen itself regulates these receptors depending on the phase of menstrual cycle and age of the patient. Hence, estrogen treatment has profound effect on regulation of estrogen receptors thereby decreasing the major fluctuations.Estrogen receptors(ER) have protective effect on vasculature by production of Nitric Oxide(NO). Regulation of expression of these ER by mainly E2 plays a vital role in preventing aneurysmal growth and rupture.[19,20]

GPER:-

A G-protein coupled estrogen receptor (GPER) is widely distributed in brain and cerebral vasculature. E2 has strong affinity to this receptor which is totally unrelated to traditional estrogen receptors. This GPER carries out non – genomic effects of estrogen which have regulatory role on collagen morphology of vessel wall. [19,21.]

Contributing Factors:-

In a study on Japanese women, earlier age of menarche and nulliparity were associated with increased risk of Sub arachnoid haemorrhage. Therefore sex specific hormonal factor may play a role in the pathogenesis of aneurysm formation and rupture [27,29].

The collagen that is present in the bone and skin is similar to that found in the walls of proximal segments of cerebral arteries. In post-menopausal women, there is wasting of this collagen due to estrogen deficiency. This could possibly explain for the degeneration of this collagen in the proximal segments of cerebral arteries leading to aneurysm formation.[23,28.]

Factors leading to relative deficiency of estrogen often increased the risk of aneurysm formation and SAH. But, estrogen deficiency alone is not sufficient to corroborate the hypothesis because men also show some deficiency of estrogen. So, it is not the absolute levels but dramatic changes in the estrogen levels is that which contributes to the pathogenesis. Hence men are at reduced risk because they do not experience that steep change in the levels of estrogen as it occurs at menopause. Hence periodicity in the levels of estrogen is the contributory factor.[27,29]

Harada et al found based on their observations that internal carotid artery(ICA) was more commonly involved in aneurysm formation as well as rupture in women whereas anterior cerebral artery (ACA) and middle cerebral artery (MCA) are more commonly affected by aneurysm formation in men. In men it is the hemodynamic factors that contribute to evolution of aneurysms whereas in females it is the intrinsic deficiency in the wall of vessel which is more contributory. Hence estrogen is a potential target for preventing the evolution of aneurysms in peri-menopausal women.[32]

Role of hormone replacement therapy (HRT):-

Regulation of inflammatory cascades and vascular wall integrity are the main areas where estrogen has its conducive effects. Dysregulation of this mechanism promotes growth and rupture of aneurysms. Hence , hormone replacement therapy(HRT) with E2 could be a therapeutic strategy. However, various randomized control trials have shown negative effects of HRT and the reasons could be: age related changes in ER numbers, changes in distributions of ER, down streaming of ER signaling pathways and age related changes in the collgen components in vessel walls. Estrogen cannot reverse the pre-existing vascular pathology although it can give relief from menopausal symptoms[31,32]. In various randomized control studies, HRT might not have been administered early enough so has to have conducive effect and contributing to negative effects. Hence, the time of HRT administration is vital in preventing aneurysm growth and rupture. The HRT should begin soon after the depletion of endogenous E2 to have positive effect in preventing aneurysm growth and rupture[33,35].

And coming to the mode of administration, oral HRT increases the risk of venous thrombo-embolism whereas transdermal HRT has little impact on thrombosis. And also the risks of coronary heart diseases are reduced in women who start HRT within 10 years of menopause. Other effects of HRT are : increased risk of breast cancer and meningiomas in women[35,36].

Selective estrogen receptors modulators (SERM):-

Specific estrogen agonists targeted on modulating cerebral vascular ER activity without having any other detrimental effects on other systemic circulation have been recently developed providing a boost to HRT. A superior effect of these selective estrogen receptor modulators (SERM) with favorable tissue specificity have been documented on preventing the growth and rupture of aneurysms compared to E2.[39,40]

Phytoestrogens:-

Isoflavones such as Genistein which are chiefly found in soya-bean derived products mediate estrogenic effects through ER and also GPER thereby promoting genomic and non-genomic actions on cerebral vasculature. Genistein has also conducive effects on extra-cellular matrix (ECM). ECM has vital role in regulating vascular wall integrity and remodeling and hence these provide an alternate strategy to HRT.[36,41]

Future trends:-

The current strategies of management of unruptured intracranial aneurysms is controversial. Medical management is largely limited to: smoking cessation, control of blood pressure, radiological surveillance, neurosurgical and endo-vascular interventions. There is no documented pharmacological treatment available to decrease the risk of aneurysm growth and rupture. Pathophysiology based therapies like HRT, SERMS and Phytoestrogens may play a vital role in preventing rupture of intracranial aneurysms in post-menopausal women thereby reducing the morbidity and mortality due to SAH in this segment of population.[2,9,42]

New generation HRT, SERMS and Phytoestrogens may have beneficial role in prevention of rupture of aneurysms if initiated at right timing of peri-menopausal women diagnosed with having small un-ruptured aneurysms. Although conducive effects of these agents are much less in older women due to pre-existing cerebrovascular diseases and cardiovascular pathologies, future investigations are needed to devise novel strategies. Appropriate route of administration, dosage, periodicity of administration and timing of administration provide a pragmatic approach for increasing the benefits of these therapies and subsequent preventing the growth and rupture of aneurysms causing SAH.[49,50]

Conclusion:-

Estrogen deficiency has a significant impact on the pathophysiology of aneurysmal rupture and SAH. An understanding of this subtle relationship between estrogen and SAH might have significant implication on women's health.

References:-

1. J. van Gijn, R. S. Kerr, and G. J. Rinkel, "Subarachnoid haemorrhage," The Lancet, vol. 369, no. 9558, pp. 306–318, 2007. View at Publisher · View at Google Scholar · View at Scopus
2. J. C. Torner, "Epidemiology of subarachnoid hemorrhage," Seminars in Neurology, vol. 4, no. 03, pp. 354–369, 1984. View at Publisher · View at Google Scholar
3. C. Ayala, J. B. Croft, K. J. Greenlund et al., "Sex differences in US mortality rates for stroke and stroke subtypes by race/ethnicity and age, 1995–1998," Stroke, vol. 33, no. 5, pp. 1197–1201, 2002. View at Publisher · View at Google Scholar · View at Scopus
4. J. R. Ostergaard and E. Hog, "Incidence of multiple intracranial aneurysms. Influence of arterial hypertension and gender," Journal of Neurosurgery, vol. 63, no. 1, pp. 49–55, 1985. View at Publisher · View at Google Scholar · View at Scopus
5. S. Juvela, K. Poussa, and M. Porras, "Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study," Stroke, vol. 32, no. 2, pp. 485–491, 2001. View at Publisher · View at Google Scholar · View at Scopus
6. M.-H. Li, S.-W. Chen, Y.-D. Li et al., "Prevalence of unruptured cerebral aneurysms in Chinese adults aged 35 to 75 years: a cross-sectional study," Annals of Internal Medicine, vol. 159, no. 8, pp. 514–521, 2013. View at Publisher · View at Google Scholar · View at Scopus
7. K. Harada, K. Fukuyama, T. Shirouzu et al., "Prevalence of unruptured intracranial aneurysms in healthy asymptomatic Japanese adults: differences in gender and age," ActaNeurochirurgica, vol. 155, no. 11, pp. 2037–2043, 2013. View at Publisher · View at Google Scholar · View at Scopus
8. L. Zhao, L. Zhang, X. Zhang, Z. Li, L. Tian, and Y.-X. J. Wang, "An analysis of 1256 cases of sporadic ruptured cerebral aneurysm in a single Chinese institution," PLoS ONE, vol. 9, no. 1, Article ID e85668, 2014. View at Publisher · View at Google Scholar · View at Scopus
9. N. K. de Rooij, F. H. H. Linn, J. A. Van Der Plas, A. Algra, and G. J. E. Rinkel, "Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends," Journal of Neurology, Neurosurgery and Psychiatry, vol. 78, no. 12, pp. 1365–1372, 2007. View at Publisher · View at Google Scholar · View at Scopus
10. C. Ding, V. Toll, B. Ouyang, and M. Chen, "Younger age of menopause in women with cerebral aneurysms," Journal of NeuroInterventional Surgery, vol. 5, no. 4, pp. 327–331, 2013. View at Publisher · View at Google Scholar · View at Scopus
11. F. H. H. Linn, G. J. E. Rinkel, A. Algra, and J. Van Gijn, "Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis," Stroke, vol. 27, no. 4, pp. 625–629, 1996. View at Publisher · View at Google Scholar · View at Scopus
12. M. H. Young, S. K. Karri, and C. S. Ogilvy, "Exploring the use of estrogen& progesterone replacement therapy in subarachnoid hemorrhage," Current Drug Safety, vol. 7, no. 3, pp. 202–206, 2012. View at Publisher · View at Google Scholar · View at Scopus
13. W. T. Longstreth Jr., L. M. Nelson, T. D. Koepsell, and G. Van Belle, "Subarachnoid hemorrhage and hormonal factors in women. A population-based case-control study," Annals of Internal Medicine, vol. 121, no. 3, pp. 168–173, 1994. View at Publisher · View at Google Scholar · View at Scopus
14. K. Okamoto, R. Horisawa, T. Kawamura et al., "Menstrual and reproductive factors for subarachnoid hemorrhage risk in women: a case-control study in Nagoya, Japan," Stroke, vol. 32, no. 12, pp. 2841–2844, 2001. View at Publisher · View at Google Scholar · View at Scopus
15. T. Stober, S. Sen, T. Anstätt, G. Freier, and K. Schimrigk, "Direct evidence of hypertension and the possible role of post-menopause oestrogen deficiency in the pathogenesis of berry aneurysms," Journal of Neurology, vol. 232, no. 2, pp. 67–72, 1985. View at Publisher · View at Google Scholar · View at Scopus
16. M. Brincat, C. F. Moniz, J. W. W. Studd, A. J. Darby, A. Magos, and D. Cooper, "Sex hormones and skin collagen content in postmenopausal women," British Medical Journal, vol. 287, no. 6402, pp. 1337–1338, 1983. View at Publisher · View at Google Scholar · View at Scopus
17. J. L. Bolognia, I. M. Braverman, M. E. Rousseau, and P. M. Sarrel, "Skin changes in menopause," Maturitas, vol. 11, no. 4, pp. 295–304, 1989. View at Publisher · View at Google Scholar · View at Scopus
18. J. A. Baron, C. La Vecchia, and F. Levi, "The antiestrogenic effect of cigarette smoking in women," American Journal of Obstetrics and Gynecology, vol. 162, no. 2, pp. 502–514, 1990. View at Publisher · View at Google Scholar · View at Scopus

19. T. Horiuchi, Y. Tanaka, and K. Hongo, "Sex-related differences in patients treated surgically for aneurysmal subarachnoid hemorrhage," Neurologia Medico-Chirurgica, vol. 46, no. 7, pp. 328–332, 2006. View at Publisher · View at Google Scholar · View at Scopus
20. K. Igase, I. Matsubara, M. Igase, H. Miyazaki, and K. Sadamoto, "Initial experience in evaluating the prevalence of unruptured intracranial aneurysms detected on 3-tesla MRI," Cerebrovascular Diseases, vol. 33, no. 4, pp. 348–353, 2012. View at Publisher · View at Google Scholar · View at Scopus
21. M. H. M. Vlak, A. Algra, R. Brandenburg, and G. J. E. Rinkel, "Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis," The Lancet Neurology, vol. 10, no. 7, pp. 626–636, 2011. View at Publisher · View at Google Scholar · View at Scopus
22. M. Aarhus, C. A. Helland, and K. Wester, "Differences in anatomical distribution, gender, and sidedness between ruptured and unruptured intracranial aneurysms in a defined patient population," ActaNeurochirurgica, vol. 151, no. 12, pp. 1569–1574, 2009. View at Publisher · View at Google Scholar · View at Scopus
23. T. Inagawa, "Site of ruptured intracranial saccular aneurysms in patients in Izumo City, Japan," Cerebrovascular Diseases, vol. 30, no. 1, pp. 72–84, 2010. View at Publisher · View at Google Scholar · View at Scopus
24. G. L. Kongable, G. Lanzino, T. P. Germanson et al., "Gender-related differences in aneurysmal subarachnoid hemorrhage," Journal of Neurosurgery, vol. 84, no. 1, pp. 43–48, 1996. View at Publisher · View at Google Scholar · View at Scopus
25. M. W. Vernooij, M. A. Ikram, H. L. Tanghe et al., "Incidental findings on brain MRI in the general population," The New England Journal of Medicine, vol. 357, no. 18, pp. 1821–1828, 2007. View at Publisher · View at Google Scholar · View at Scopus
26. M. Chen, B. Ouyang, L. Goldstein-Smith, and L. Feldman, "Oral contraceptive and hormone replacement therapy in women with cerebral aneurysms," Journal of NeuroInterventional Surgery, vol. 3, no. 2, pp. 163–166, 2011. View at Publisher · View at Google Scholar · View at Scopus
27. T. Mizutani, Y. Miki, H. Kojima, and H. Suzuki, "Proposed classification of nonatherosclerotic cerebral fusiform and dissecting aneurysms," Neurosurgery, vol. 45, no. 2, pp. 253–260, 1999. View at Publisher · View at Google Scholar · View at Scopus
28. R. H. Sacho, G. Saliou, A. Kostynskyy, et al., "Natural history and outcome after treatment of unrupturedintradural fusiform aneurysms," Stroke, vol. 45, no. 11, pp. 3251–3256, 2014. View at Publisher · View at Google Scholar · View at Scopus
29. J. C. Serrone, Y. M. Gozal, A. W. Grossman et al., "Vertebrobasilar fusiform aneurysms," Neurosurgery Clinics of North America, vol. 25, no. 3, pp. 471–484, 2014. View at Publisher · View at Google Scholar · View at Scopus
30. G. A. Holzapfel, T. C. Gasser, and R. W. Ogden, "A new constitutive framework for arterial wall mechanics and a comparative study of material models," Journal of Elasticity, vol. 61, no. 1–3, pp. 1–48, 2000. View at Publisher · View at Google Scholar · View at Scopus
31. T. Eriksson, M. Kroon, and G. A. Holzapfel, "Influence of medial collagen organization and axial in situ stretch on saccular cerebral aneurysm growth," Journal of Biomechanical Engineering, vol. 131, no. 10, Article ID 101010, 2009. View at Publisher · View at Google Scholar · View at Scopus
32. S. Kondo, N. Hashimoto, H. Kikuchi, F. Hazama, I. Nagata, and H. Kataoka, "Apoptosis of medial smooth muscle cells in the development of saccular cerebral aneurysms in rats," Stroke, vol. 29, no. 1, pp. 181–188, 1998. View at Publisher · View at Google Scholar · View at Scopus
33. H. Handa, N. Hashimoto, I. Nagata, and F. Hazama, "Saccular cerebral aneurysms in rats: a newly developed animal model of the disease," Stroke, vol. 14, no. 6, pp. 857–866, 1983. View at Publisher · View at Google Scholar · View at Scopus
34. J. D. Robinson, H. L. Judd, P. E. Young, O. W. Jones, and S. S. Yen, "Amniotic fluid androgens and estrogens in midgestation," Journal of Clinical Endocrinology and Metabolism, vol. 45, no. 4, pp. 755–761, 1977. View at Publisher · View at Google Scholar · View at Scopus
35. T. Lind, E. C. Cameron, W. M. Hunter et al., "A prospective, controlled trial of six forms of hormone replacement therapy given to postmenopausal women," British Journal of Obstetrics and Gynaecology, vol. 86, supplement 3, pp. 1–29, 1979. View at Google Scholar · View at Scopus
36. J. Calleja-Agius and M. Brincat, "The effect of menopause on the skin and other connective tissues," Gynecological Endocrinology, vol. 28, no. 4, pp. 273–277, 2012. View at Publisher · View at Google Scholar · View at Scopus

37. Y. M. Baron, R. Galea, and M. Brincat, "Carotid artery wall changes in estrogen- treated and -untreated postmenopausal women," Obstetrics and Gynecology, vol. 91, no. 6, pp. 982–986, 1998. View at Publisher · View at Google Scholar · View at Scopus
38. L. M. Kadasi, W. C. Dent, and A. M. Malek, "Cerebral aneurysm wall thickness analysis using intraoperative microscopy: effect of size and gender on thin translucent regions," Journal of NeuroInterventional Surgery, vol. 5, no. 3, pp. 201–206, 2013. View at Publisher · View at Google Scholar · View at Scopus
39. R. A. Khalil, "Estrogen, vascular estrogen receptor and hormone therapy in postmenopausal vascular disease," Biochemical Pharmacology, vol. 86, no. 12, pp. 1627–1642, 2013. View at Publisher · View at Google Scholar · View at Scopus
40. C. J. Gruber, W. Tschugguel, C. Schneeberger, and J. C. Huber, "Production and actions of estrogens," The New England Journal of Medicine, vol. 346, no. 5, pp. 340–352, 2002. View at Publisher · View at Google Scholar · View at Scopus
41. C. Stirone, S. P. Duckles, and D. N. Krause, "Multiple forms of estrogen receptor-α in cerebral blood vessels: regulation by estrogen," The American Journal of Physiology—Endocrinology and Metabolism, vol. 284, no. 1, pp. E184–E192, 2003. View at Publisher · View at Google Scholar · View at Scopus
42. K. H. Kim and J. R. Bender, "Membrane-initiated actions of estrogen on the endothelium," Molecular and Cellular Endocrinology, vol. 308, no. 1-2, pp. 3–8, 2009. View at Publisher · View at Google Scholar · View at Scopus
43. G. Kalesnykas, U. Roschier, J. Puoliväli, J. Wang, and R. Miettinen, "The effect of aging on the subcellular distribution of estrogen receptor-alpha in the cholinergic neurons of transgenic and wild-type mice," European Journal of Neuroscience, vol. 21, no. 5, pp. 1437–1442, 2005. View at Publisher · View at Google Scholar · View at Scopus
44. V. M. Miller and S. P. Duckles, "Vascular actions of estrogens: functional implications," Pharmacological Reviews, vol. 60, no. 2, pp. 210–241, 2008. View at Publisher · View at Google Scholar · View at Scopus
45. C. M. Revankar, D. F. Cimino, L. A. Sklar, J. B. Arterburn, and E. R. Prossnitz, "A transmembrane intracellular estrogen receptor mediates rapid cell signaling," Science, vol. 307, no. 5715, pp. 1625–1630, 2005. View at Publisher · View at Google Scholar · View at Scopus
46. Y. Tada, H. Makino, H. Furukawa et al., "Roles of estrogen in the formation of intracranial aneurysms in ovariectomized female mice," Neurosurgery, vol. 75, no. 6, pp. 690–695, 2014. View at Publisher · View at Google Scholar · View at Scopus
47. Y. Tada, K. Wada, K. Shimada et al., "Estrogen protects against intracranial aneurysm rupture in ovariectomized mice," Hypertension, vol. 63, no. 6, pp. 1339–1344, 2014. View at Publisher · View at Google Scholar · View at Scopus
48. J. Lin, C. Steenbergen, E. Murphy, and J. Sun, "Estrogen receptor-beta activation results in S-nitrosylation of proteins involved in cardioprotection," Circulation, vol. 120, no. 3, pp. 245–254, 2009. View at Publisher · View at Google Scholar · View at Scopus
49. F. Naftolin, H. P. G. Schneider, and D. W. Sturdee, "Guidelines for hormone treatment of women in the menopausal transition and beyond," Climacteric, vol. 7, no. 4, pp. 333–337, 2004. View at Publisher · View at Google Scholar · View at Scopus
50. M. E. Mendelsohn and R. H. Karas, "HRT and the young at heart," The New England Journal of Medicine, vol. 356, no. 25, pp. 2639–2641, 2007. View at Publisher · View at Google Scholar · View at Scopus
51. D. A. Schreihofer and Y. Ma, "Estrogen receptors and ischemic neuroprotection: who, what, where, and when?" Brain Research, vol. 13, no. 1514, pp. 107–122, 2013. View at Publisher · View at Google Scholar · View at Scopus