



Opinion

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Cardioprotection: A Neo-Perspective for Clinical Implication of Nestorone®



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Opinion

Nestorone or Segesterone acetate is a fourth-generation progestin [1] and patented by the Population Council Inc., New York, USA. Progestins (Progestogens) are synthetic compounds developed to imitate the actions of the natural hormone Progesterone. From the studies, Nestorone is observed to be a "pure progestational molecule", and very potent progestin with high progestational activity [2-5]. It doesn't exhibit androgenic or anabolic activity [4]. Moreover, it is neither estrogenic nor uterotrophic entity [4]. It does not affect serum lipid levels or carbohydrate metabolism in women [6]. Nestorone does not show glucocorticoid activity. Not only that, it does not bind to sex hormone binding globulin (SHBG) [7]. Thus, it has a shorter half-life and high metabolic clearance rates (MCR). Therefore, it is unassailable (invulnerable) to use as a contraceptive in breastfeeding mothers [4]. Thus, considering its peculiar properties, Nestorone was primarily used in female contraception and hormone replacement therapy (HRT) successfully [4]. In recent years, its potential utilities in the male contraception and neuroprotection were also established [5].

Once Sir Isaac Newton said "It is the weight, not numbers of experiments that is to be regarded" [8]. Yes, he was absolutely right in saying so because the quality of any person or new chemical entity (NCE) is regarded, not the quantity. Qualities are accessed using multiple parameters. Thus, considering aforementioned multiple pharmacological qualities of Nestorone, a NCE, we must strive to elucidate its role on Cardiovascular System. Because it is well known fact that females have protection from hypertension and coronary heart diseases during the reproductive phase of their life which disappears after menopause [9-17]. Therefore, it is contemplated that female sex hormones, viz., Estrogen and Progesterone are mainly responsible for the same. However, the exact mechanism of cardioprotection remains enigmatic [18]. It is also well-established fact that Progesterone receptors are found in blood vessels/ arterial walls and in the endothelial cell lining the walls [19,20]. Therefore, it is very logical and plausible

to hypothesize that Progesterone must be having unavoidable roles in the cardiovascular health and diseases (CHD). Recently, Dharwadkar and her colleagues [18] have provided an exclusive new perspective theory of cardioprotection as a function of progesterone induced respiratory alkalosis, decreased plasma ionic calcium concentration and generalized vasodilatation. It explicitly explained the lack of cardioprotection in the absence of Progesterone in postpartal and postmenopausal women [18]. Moreover, some progestins used in contraception and HRT are reported to exert cardiovascular effects [3, 19,21-25]. There are reports of HRT that Medroxyprogesterone acetate (a progestin widely prescribed in the USA) inhibited 50% of coronary dilatory response exhibited by Estrogen [26,27]. Thus, it seemed that the cardiovascular effects of progestins may influence the cardioprotective effect of estrogens. So, a combined estrogen-progestin therapy may mitigate some of estrogen's beneficial effects on cardiovascular health. Some studies found that progestins reduced the beneficial effect of estrogens, while others did not. In 2001, Rosano and Fini's team of investigators [19] has shown that different estrogen-progestin treatments have different effects upon vascular reactivity and that a careful selection of the progestin to be added to estrogen is of crucial importance to preserve, or even enhance the positive vascular effects of estrogens [19]. Apart from these, Fu et al. [28] reported the actions of different Progestins viz., Progesterone, Medroxyprogesterone Acetate, Drospirenone and Nestorone on breast cancer cells, and supported the concept that each progestin acts differently on the same target cells (breast cancer cells). Considering these very few trivial and inconclusive data available on the vascular effect of progestins in menopausal women and other diseases, it would be worthy to investigate the relevant clinical implications of Nestorone on the Cardiovascular System. It's role can also be elucidated in the development, progression and/ or prevention of Progesterone-dependant Cancers. As Nestorone is a high affinity agonist for progesterone receptor, thus, it is unequivocal to say that Nestorone could also play a

significant role on Cardiovascular System. Therefore, it would be worthy to elucidate the roles of Nestorone in cardioprotection (in particular) and on Cardiovascular System, in general. This sort of studies would also provide insight and add to unravel the mechanism of how the natural hormone Progesterone plays versatile roles in the body, in a proper coordination to control multiple physiological functions. There seems to be every possibility that Nestorone could emerge as a cardioprotective agent, as well. It's efficiency in cardio protection, however, remains to be thoroughly investigated.

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