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## Progesterone and cardiovascular disease

**International guidelines do not recommend the use of hormone replacement therapy (HRT) as a means to reduce cardiovascular risk in postmenopausal women with or without previous heart disease.<sup>1</sup> On issuing their recommendations, current guidelines have taken into account the outcomes of large, randomized, controlled trials, which, contrary to previous observational studies, have failed to demonstrate a beneficial effect of HRT on cardiovascular risk.**

As a result, hormone replacement therapy has been abandoned for cardiac risk reduction, whether as a primary or secondary preventative measure. However, the question emerges as to whether this blanket condemnation of female hormones represents a sensible action or a disproportionate overreaction. The present article briefly addresses this issue, particularly in relation to whether progesterone should be included in the same category as progestins. Confusion exists in the medical literature regarding the cardiovascular effects of progesterone, compared with those of estrogen and the synthetic progestin medroxyprogesterone acetate (MPA). Content in this brief article is mainly based on data recently published by Hermesmeyer et al.<sup>2</sup>

### Differences between the cardiovascular actions of estrogen, progestins, and progesterone

Estrogen and MPA are widely prescribed in combination for HRT. In a recent review article, Hermesmeyer et al<sup>2</sup> have highlighted the semantic confusion that has possibly contributed to the existing confusion regarding the relative risks and benefits of the administration of progestins to postmenopausal women in relation to cardiovascular disease prevention. Some of the confusion has been generated by the frequent use of the terms "progesterone" and "progestin" as synonymous. There is only one, naturally occurring progesterone, which belongs to the class of substances known as "progestins."<sup>3</sup> Thus although many "progestins" exist, there is only one "progesterone."<sup>2</sup>

Although several trials assessing the cardiovascular effects of female hormones have claimed to be "progesterone trials," they have in fact been "progestin trials," as physiological progesterone was not used in these studies.<sup>2</sup> The cardiovascular actions of progesterone are relatively well known, but there is a lack of knowledge regarding the actions of synthetic progestins such as MPA. Different progestins have different cardiovascular actions.<sup>4</sup> Of interest, they can even have almost opposite effects on some organs or systems. For example, whilst MPA and progesterone have similar antiproliferative progestogenic actions on the endometrium, their cardiovascular effects differ markedly, with progesterone exerting a more "cardioprotective" action compared with MPA.<sup>5,6</sup> Indeed, progesterone has been reported to improve cardiovascular function, whilst MPA and other synthetic progestins have not been shown to have beneficial actions on the cardiovascular system.<sup>7,8</sup> Contrary to MPA, progesterone inhibits the expression of

cell adhesion molecule-1 in endothelial cells, a molecule involved in atherogenesis and atherosclerotic disease progression.<sup>9</sup>

### Lessons from large randomized trials

As stated by Hermesmeyer et al,<sup>2</sup> the Heart and Estrogen/progestin Replacement Study (HERS),<sup>10</sup> the Women's Health Initiative (WHI) study,<sup>11,12</sup> and Women's International Study of long-Duration Oestrogen after Menopause (WISDOM)<sup>13</sup> have refuted the cardiovascular benefits of HRT. However, the results of these large trials should not be interpreted as confirmation that progesterone is harmful. All of these trials used synthetic progestins, and only in combination with Premarin® (a conjugated estrogen; Wyeth, Madison, NJ). Specifically, all used Prempro®, or its cyclic treatment variant Premphase® (Wyeth), both of which consist of conjugated estrogen and a high concentration of MPA (2.5 mg/day). The only large, randomized, controlled Premarin® trial that included progesterone as well as MPA was in the arms of the Postmenopausal Estrogen/Progestin Intervention (PEPI) study where menopausal women without a uterus received Premarin® only, without any progestin.<sup>14</sup> The study found that, in terms of the primary end point of the study ie, raising HDL cholesterol, micronized progesterone was significantly better than MPA.<sup>14</sup> In the Progesterone Treatment of Blunt Traumatic Brain Injury (ProTECT) prospective study, intravenous progesterone treatment (without estrogen) showed beneficial effects, including a reduced 30-day mortality compared with placebo.<sup>15</sup> As highlighted by Hermesmeyer et al,<sup>2</sup> progesterone, alone or combined with estrogen, has never been prospectively tested as a potential agent to prevent cardiovascular disease and its complications. Moreover, data from large, randomized, controlled trials are needed to assess the effects of progesterone on endothelial function, coronary blood flow, and cardiovascular prevention in humans.

**In conclusion, based on existing experimental work and observational studies, progesterone clearly appears to have beneficial effects on the cardiovascular system, but this notion needs to be objectively explored in large, well-designed prospective studies. It is only via rigorous research that we will be able to determine whether progesterone, with or without estrogen, has a role in reducing cardiovascular risk in postmenopausal women.**

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