Main safety issues in HRT - Which choice of the progestogen?

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In HRT adequate progestogen addition urgently is recommended in women with intact uterus. The primary indication to use a progestogen in HRT is endometrial protection from unopposed estrogen therapy. Progestogen is not generally indicated with estrogen therapy post hysterectomy. Progestogens should have high endometrial efficacy protecting the endometrium from estrogen induced hyperproliferation which could lead via hyperplasia to endometrial cancer. Clinically the addition to estrogen replacement should lead to regular bleeding pattern in sequential HRT and rapid amenorrhoe in continuous combined HRT. In addition the most important criteria for the choice of a progestogen in HRT is tissue neutrality - no proliferation effects in the breast, neutral in the vasculature and in the metabolic system maintaining beneficial effects in lipids and glucose metabolism. Progesterone, the physiological progestogen, mostly meets those criteria, and also its retroisomer dydrogesterone, which has stronger endometrial efficacy. In contrast to various synthetic progestogens these more physiological progestogens do not further increase the estrogen induced risk of venous thromboembolism, they do not antagonize the cardiovascular benefit of estrogens, and they may not increase the risk of breast cancer at least up to 8 years treatment, derived from clinical data and main mechanisms of carcinogenicity. A recent Editorial of the journal "Menopause" suggested that the increase in breast risk in WHI could be explained by overexpression of certain membrane-bound steroid receptors. Own work showed that progesterone does not, in contrast to most synthetic progestogens. Other benefits of certain progestogens like the potency of drosperinone to maintain or even decrease the blood pressure can be considered at an individual basis, e.g. in cardiovascular risk patients, but are of secondary importance.

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