Tachyphylaxis

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Tachyphylaxis is a 'rapid decrease in response to repeated doses of a drug over time' (1). In other words, a sudden loss of drug efficacy, causing symptoms to reappear that are unresponsive to higher doses.

Concerns that HRT can cause tachyphylaxis are based on a single study published in 1990, in which oestradiol levels were measured in 1388 women treated with subcutaneous oestrogen implants (2). Subcutaneous implants are usually inserted every 6 months, but 3% of the women reported that their symptoms started to return after just 4 months, and they needed more frequent implant insertions. Four monthly implant insertions were associated with higher oestrogen levels, but these women did not have true tachyphylaxis because symptom control was achieved with the higher (more frequent) doses. The authors noted that women with a history of PMS and severe depression, and women who had undergone surgical menopause, were more likely to benefit from high doses, and concluded that 'higher doses may be necessary to achieve symptom control in some women'. The authors did not consider this to be an example of tachyphylaxis, but unfortunately the study has since been repeatedly cited as evidence for this phenomenon in women who use HRT.

In 2019 a case study was published in which a 47-year-old woman presented to a menopause clinic with a recurrence of her menopausal symptoms despite using 4 pumps of gel (3). She was found to have an oestradiol level of 1052 - a normal mid-cycle oestradiol level in a perimenopausal woman. High levels can also occur erratically in the perimenopause, and/or result from contamination in women using oestrogen gel (4), which is why blood tests can be misleading and shouldn’t be relied upon. The authors speculated that this woman’s oestradiol level might be indicative of tachyphylaxis, but there were other possible reasons for her symptoms including an inadequate dose and non-hormonal factors. The patient's HRT dose was reduced which may have led to the subsequent fall in her oestradiol level, and she continued to experience symptoms on the lower dose. A case study is not a scientific study and does not demonstrate causality.

Otherwise, there hasn't been a single study that has reported tachyphylaxis in women using HRT. Plasma oestradiol levels increase approximately 100-fold during pregnancy and reach 70,000 pmol/L in some women. Pregnancy is not associated with tachyphylaxis.

Approximately 1 in 4 women have subtherapeutic oestrogen levels using standard licensed HRT doses, either because they are 'poor absorbers' or 'fast metabolisers', meaning that many women need higher doses to achieve adequate symptom control. Some women need higher doses because they benefit from having higher oestrogen levels, possibly due to differences in tissue sensitivity. This may be especially true for some women suffering with severe psychological symptoms (5), as noted in the early study cited above (2). Higher doses are also more beneficial for bone health (6). There is no evidence that higher doses of transdermal oestrogen, or higher circulating oestrogen levels, are associated with long-term harm in women who feel clinically well.

Guidelines recommend that the oestradiol dose is individualised, because all women are different and clinical response is variable (7). Failure to individualise care, and subtherapeutic doses, cause unnecessary suffering for women and increase the risk of long-term harms such as cardiovascular disease and osteoporosis. There is no evidence to suggest that higher oestradiol doses cause tachyphylaxis, and this should not be used as a reason to reduce the dose. A holistic, personalised approach that includes titrating the dose to the clinical response is the cornerstone of high-quality menopause care.

References

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