# Bleeding and HT

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**What bleeding patterns can I expect when taking HT?**

Providing estrogen alone to the postmenopausal woman with an intact uterus is associated with an increased incidence of hyperplasia and endometrial cancer. It is therefore fundamental, in the overwhelming majority of cases, to add progestogens to estrogen when managing her menopausal symptoms. Provided appropriate doses and duration of progestogens are used, their addition has successfully eliminated almost all the increased risk of endometrial hyperplasia. Unfortunately, the combination of estrogen plus a progestogen will result in vaginal bleeding, either as a menstrual period, (planned as in those patients given cyclical or sequential HT), or unplanned, (as in those patients given continuously combined regimens). A number of HT regimens do exist which offer clinicians and patients not only choice, but also flexibility, while allowing maximum health benefits. In the traditional sequential or cyclical HT regimen, estrogen is given daily, while the progestogen is given for 10-14 days in a cyclical pattern thereby producing predictable withdrawal bleeding. The use of continuously combined HT, consisting of estrogen and a progestogen taken daily is increasing. Its benefits extend not only to improving menopausal symptoms, urogenital atrophy and ensuring preservation of bone strength, but this regimen will also prevent endometrial hyperplasia and lead to amenorrhoea over time in the majority of cases.

Several studies have compared bleeding patterns obtained with continuously combined and sequential regimens. Approximately 85 - 90% of patients on sequential HT will have regular monthly withdrawal bleeding, although approximately 3 - 5% will have some form of abnormal bleeding, whilst 15% will cease to have periods after 5 years of use. Initial bleeding on continuously combined HT is irregular and unpredictable. Approximately 40% of patients will develop spotting or fresh vaginal bleeding within the first 6 - 9 months. Beyond 6 - 9 months over 85% of the patients will be amenorrhoeic. An onset of menopause more than one year before study entry is associated with less bleeding than onset within one year i.e. to minimise spotting or abnormal vaginal bleeding, patients must be more than one year into their menopause before continuously combined HT is used.

A concept that has recently been receiving overwhelming support is that of low dose HT. This ideally not only provides all the known beneficial effects of conventional HT, but minimises the adverse effects. From a bleeding point of view, the lower the estrogen dose, the lower the required progestogen dosage to protect the endometrium. Lower dose estrogen-progestogen schedules can virtually end endometrial proliferation and, when administered in a continuously combined fashion, is very effective in preventing abnormal bleeding. Even though abnormal bleeding is seen initially with low dose preparations, its occurrence and duration are significantly less than with conventional dose HT. This applies even when the low dose continuously combined HT is started in patients <1 year after onset of menopause. The long cycle HT, i.e. withdrawal bleeds only every 3 months, although preferred by most women, may lead to unacceptable levels of endometrial hyperplasia and should not be first-line therapy. Abnormal bleeding is certainly not product specific, and although different formulations of estrogen and progestogen may differ in their effect on the endometrium, it is purely speculative to comment on which formulation is more likely to be "better" from a bleeding point of view. Each progestogen certainly has a different biological profile, norethindrone being a more potent progestogen than either medroxyprogesterone acetate (MPA) or progesterone. Nevertheless, from the data available, most commercially available continuously combined HT products will cause abnormal bleeding which generally, in the overwhelming majority of cases, will subside after 6 - 9 months.

**Will bleeding ever stop if I am taking HT?**

The primary aim in providing patients with cyclical or sequential regimens is to ensure withdrawal bleeding on a monthly basis. This will occur in approximately 85 - 90% of cases, but

in approximately 10 - 15% of patients, amenorrhoea will result after 5 years or more use.

Several studies have confirmed that an atrophic endometrium is achieved with continuing combined HT in 90 - 100% of women even after 3 months of treatment, but more obviously so after 6 months or more, with daily doses of progestogen as low as 0.35 mg norethisterone acetate or 2.5 mg MPA. Even though conventional dose continuously combined HT offers the prospect of inducing amenorrhoea over time, low dose continuously combined HT provides a greater likelihood of this occurring, whereby >95% will be amenorrhoeic after 3 months use.

**Does HT cause cancer of the lining of the womb?**

In clinical situations we assume that inhibition of endometrial hyperplasia implies endometrial protection. To date all clinical trials of unopposed estrogen at moderate or high doses have shown an increase in the incidence of endometrial hyperplasia. This is related to dose and duration, i.e. after 2 years of unopposed estrogen there is a 10 fold increase in likelihood of endometrial cancer. Furthermore, it is also reported that the risk remains increased for many years after stopping the therapy, i.e. up to 15 years later. As stated previously, it is therefore the "gold standard" that estrogen supplementation must always be opposed with progestogens in women who have an intact uterus. Data pertaining to sequential HT indicate that progestogen will reduce the risk of endometrial hyperplasia and cancer. The duration of progestogen in each cycle is important and should be for at least 10 days, preferably 12 - 14 days, although there may still be a risk with use beyond 5 years where the relative risk increases to 2.5 compared to non-users. The rate of endometrial hyperplasia was not shown to be different for continuously combined HT and placebo in a Cochrane meta-analysis. The biochemical and morphological changes in the endometrium induced by the administration of progestogens are maintained as long as the progestogen is administered. If this is continuous, the proliferative effect of the estrogen will be prevented and the endometrium should remain atrophic. Endometrial cancer is a most unlikely and uncommon occurrence in women taking continuously combined HT and, in those described, there was a history of unopposed estrogen usage or sequential HT use with less than 10 days of progestogens or risk factors such as family history of endometrial cancer. Five years or more of continuously combined HT decreased the risk of endometrial cancer to between 0.2 - 0.8. The Women's Health Initiative study likewise further confirmed the protective effect of continuously combined HT.

**Should I be screened for cancer if I start bleeding on HT?**

All women on unopposed estrogen therapy who are bleeding must be investigated. The longer the patient remains on estrogen only, the greater the likelihood that hyperplasia will develop. Prolonged irregular bleeding in postmenopausal women on unopposed estrogen is suggestive of endometrial hyperplasia, whereas irregular bleeding experienced by women on a continuously combined regimen is not predictive of hyperplasia. Abnormal bleeding in patients on sequential HT has also been extensively investigated and there does not appear to be a correlation between endometrial histology and the day of onset of bleeding. The prevalence of endometrial hyperplasia is low, varying between 2.4% if the bleed occurs after 10 days of progestogens, and 2.8% after 12 days of progestogens.

Abnormal bleeding or spotting is common in women on continuously combined HT during the first 6 months of commencing the medication. The patient should be reassured and encouraged to persist with the medication. However, if the bleeding persists beyond 6 months of initiation or occurs after a period of 6 months of amenorrhoea, it should be investigated, bearing in mind that the chances of malignancy are extremely unlikely and that the most likely causes are atrophy of the endometrium, endometrial polyps or fibroids. Endometrial cancer in users of continuously combined HT is extremely uncommon.

Assessment of these women has entailed ultrasound imaging of the endometrium, hysteroscopy, diagnostic dilatation and curettage and endometrial assessment through biopsy. The accuracy of ultrasonography in diagnosing endometrial disease in these patients is open to question and endometrial sampling should be done as the method of excluding endometrial disease. For this, the Z-sampler or the pipelle may be used and only hysteroscopy and/or dilatation and curettage included if the bleeding persists.

**Does HT restore fertility and should I also take contraceptives when I'm on HT?**

HT in any formulation or mode of delivery will not restore fertility in a truly menopausal woman. An FSH level >40 mIU/l will exclude the likelihood of pregnancy, although even a level >25 mIU/l is most unlikely to be associated with ovulation. Nevertheless, it is important to bear in mind that HT is not a contraceptive and unless the FSH confirms true menopause, conventional contraceptive measures are needed.

*References available on request*