To advance the onset of menstrual flow 5 mg. of ENOVID should be given daily beginning on day 5 of the cycle. A ten-day course should be used and the drug discontinued. The menstrual flow should be expected about three days later. With this therapy the anticipated menstrual flow may be advanced ten days in a twenty-eight-day cycle.

Test for Pregnancy

The administration of ENOVID to a patient who is pregnant will provide endometrial support which is only additional to her endogenous hormones. On the other hand, the discontinuance of ENOVID in a patient who is not pregnant will withdraw her sole endometrial support and a bleeding episode will result. This use of the drug makes it possible to distinguish between amenorrhea due to pregnancy and that due to other causes.

Recommended Use. In this use, it is recommended that 10 mg. of ENOVID be given daily for four days. A positive finding is made if withdrawal bleeding does not occur two or three days after the four daily doses have been given.

Contraindications

1. *Pre-existing Genital or Breast Carcinoma, with Some Exceptions.* The possibility of exogenous estrogens acting as inciting agents in some cases of carcinoma of the breast or genital tract is a subject of controversy among authorities. Since ENOVID exerts estrogenic activity, the presence of carcinoma in either of these areas should be ruled out before therapy is instituted.

2. *Pre-existing Liver Disease, Dysfunction or Jaundice.* In suspected or overt liver dysfunction or disease ENOVID should not be used. The status of liver function in ENOVID-treated patients must be followed closely.

3. *Previous Thrombophlebitis or Pulmonary Embolism.* ENOVID and ENOVID-E are contraindicated in these patients unless the reason for its use in the judgment of the physician is overwhelming.

Precautions

For prevention of conception the drug is only recommended for periods of use up to four years. Longer-term use has not yet been established as safe.

At the discretion of the attending physician, during this period the drug should be used primarily when pregnancy is contraindicated or should be avoided.

Multiple detectable functional changes in the endocrine system with particular reference to the thyroid, adrenal and pituitary glands and perhaps the ovary occur in ENOVID-treated patients. The long-term effect on the pituitary, adrenal and thyroid glands and on liver metabolism is not yet clearly established although observations made on long-term users of ENOVID reveal some changes (discussed later). The present experience indicates that endocrine function typical for the individual patient prior to treatment with ENOVID returns promptly when medication is stopped.

The first intermenstrual interval after discontinuing ENOVID therapy is usually prolonged; thus a patient for whom a twenty-eight-day cycle is usual might not menstruate for thirty-five days or longer. Ovulation in such prolonged cycles will occur correspondingly later in the cycle. Succeeding cycles, however, are usually typical for the individual patient prior to therapy with ENOVID. Occasionally amenorrhea or menstrual irregularities persist for months.

A biopsy taken late in the cycle when ENOVID is given from the fifth through the twenty-fourth day of the cycle will reveal a definitely edematous stroma containing pseudodecidual cells similar in appearance to the decidual cells seen in the endometrium of early pregnancy, increased vascular development and relatively sparse glands with scanty secretion. Because of this pseudodecidual activity, mention of ENOVID therapy should accompany biopsy specimens when sent to the pathology laboratory for examination.

The question of androgenic effects of a progestin is of importance whenever the drug is prescribed for long-term use. One case of fetal masculinization has been reported in connection with ENOVID administration, but the author later stated that the incident was probably coincidental. Clinically, ENOVID has manifested no evidence of androgenicity and, in fact, is estrogenic and progestational in its actions. Nevertheless, the physician should take these reports into account when prescribing the drug.

Early reports that cervical erosion was worsened by ENOVID therapy have not been substantiated by subsequent investigation. However, patients receiving ENOVID should receive periodic vaginal examinations and any cervical erosion found should be treated by accepted means.

Patients on ENOVID therapy may show an increase in protein bound iodine and butanol extractable iodine and a decrease in T^3 values. These results do not necessarily correlate with any change in the clinical state of these patients regarding thyroid function and may reflect an increase in thyroxine binding protein similar to the increase known to follow administration of estrogens. Thyroid enlargement may occur rarely.

There is no direct evidence that ENOVID alters the diabetic state. However, in a few instances some degree of difficulty in the management of diabetic patients has been reported in connection with ENOVID therapy. It is possible that a change in insulin dosage may be required. For this reason diabetic patients should be closely observed while ENOVID is being administered. They may be expected to return to their pretreatment manageability on discontinuance of the drug.

Patients with rheumatoid arthritis receiving very high doses of ENOVID over a long period of time have been reported to show an increased bromsulphalein retention. Inconsistent and irregular moderate bromsulphalein retention has also been reported in patients receiving lower doses of ENOVID cyclically. However, preliminary investigations indicate that this has not been a significant problem. Nevertheless, cholestatic jaundice has been reported in a few instances in patients receiving ENOVID, and ENOVID will apparently induce the rare syndrome of familial jaundice of pregnancy. For this reason the administration of ENOVID to women with liver or biliary tract disease or dysfunction or a history of such disease or jaundice is contraindicated, unless the reason for such use in the opinion of the physician is overwhelming.

The status of liver function in ENOVID-treated patients must be followed closely.

It has now been accepted that one of the gonadotropin hormones of the anterior pituitary gland (the luteotropic hormone, L.T.H.) is identical to the lactogenic hormone. Since a principal action of ENOVID is the suppression of gonadotropic hormones, it is likely that ENOVID will suppress lactation if administered to a nursing mother. Suppression of lactation is less likely, however, if medication is delayed six to eight weeks post partum, when lactation is well established.

An occasional patient receiving ENOVID may experience psychic depression, although the relationship of ENOVID administration to such a response is by no means clear.

Epileptiform convulsions have been reported to occur in women receiving ENOVID. Since ENOVID may cause salt and water retention an exacerbation of