

PRESCRIBING INFORMATION

MENEST®

brand of

esterified estrogens tablets, USP

WARNINGS

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.¹⁻³ This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.⁴

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment¹ and on estrogen dose.³ In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration³; it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.^{5,6} The risk has been estimated as not greater than 4 per 1000 exposures.⁷ Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,⁸⁻¹² epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.¹³⁻¹⁶ One case control study¹⁶ estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestagens are effective for these uses. If Menest (esterified estrogens tablets) is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION

Esterified estrogens is a mixture of the sodium salts of the sulfate esters of the estrogenic substances, principally estrone, that are of the type excreted by pregnant mares. The content of total esterified estrogens is not less than 90 percent and not more than 110 percent of the labeled amount. Esterified estrogens contain not less than 75 percent and not more than 85 percent of sodium estrone sulfate, and not less than 6 percent and not more than 15 percent of sodium equilin sulfate, in such proportion that the total of these two components is not less than 90 percent, all percentages being calculated on the basis of the total esterified estrogens content.

Inactive Ingredients: Ethyl cellulose, fragrances, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, lactose, magnesium stearate, methylcellulose, polyethylene glycol, sodium bicarbonate, shellac, starch, stearic acid, titanium dioxide, and vanillin. Dyes in the form of aluminum lakes are contained in each tablet strength as follows: **0.3 mg Tablet:** FD&C Yellow No. 6, D&C Yellow No. 10. **0.625 mg Tablet:** FD&C Yellow No. 6, D&C Yellow No. 10. **1.25 mg Tablet:** FD&C Yellow No. 6, D&C Yellow No. 10, FD&C Blue No. 1. **2.5 mg Tablet:** D&C Red No. 30.

CLINICAL PHARMACOLOGY

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. They promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or nonovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens also affect the release of pituitary gonadotropins. The pharmacologic effects of esterified estrogens are similar to those of endogenous estrogens. They are soluble in water and are well absorbed from the gastrointestinal tract.

In responsive tissues (female genital organs, breasts, hypothalamus, pituitary) estrogens enter the cell and are transported into the nucleus. As a result of estrogen action, specific RNA and protein synthesis occurs. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favor excretion through the kidneys since tubular reabsorption is minimal.

INDICATIONS AND USAGE

Menest (esterified estrogens tablets) is indicated in the treatment of:

1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma - palliative therapy of advanced disease.

MENEST (esterified estrogens tablets) HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS

Estrogens should not be used in women (or men) with any of the following conditions:

1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS

1. *Induction of malignant neoplasms.* Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast¹⁸ although a recent long-term follow up of a single physician's practice has raised this possibility.^{18A} Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

2. *Gall bladder disease.* A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens,¹⁸ similar to the 2-fold increase previously noted in users of oral contraceptives.¹⁹⁻²⁴ In the case of oral contraceptives the increased risk appeared after 2 years of use.²⁴
3. *Effects similar to those caused by estrogen-progestagen oral contraceptives.* There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement are more likely to result in these adverse effects and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.²⁰⁻²³
 - a. *Thromboembolic disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.²⁴⁻³¹ Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.^{32,33} An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.^{34,35} If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.
While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found,¹⁸⁻³⁶ this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk.
Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.
Large doses of estrogen (5 mg esterified estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men³⁷ to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.
 - b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the use of oral contraceptives.³⁸⁻⁴⁰ Although benign, and rare, these may rupture and may cause death through intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestagen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.³⁹ The relationship of this malignancy to these drugs is not known at this time.
 - c. *Elevated blood pressure.* Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause⁴¹ and blood pressure should be monitored with estrogen use, especially if high doses are used.
 - d. *Glucose tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.
4. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

See footnotes at end of article.

PRECAUTIONS

A. *General Precautions:*

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pre-treatment and periodic physical examinations should include special reference to blood pressure, breast, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without another physical examination being performed.

2. Fluid retention – Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
 3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.
 4. Oral contraceptives appear to be associated with an increased incidence of mental depression.²⁴ Although it is not clear whether this is due to the estrogenic or progestagenic component of the contraceptive, patients with a history of depression should be carefully observed.
 5. Pre-existing uterine leiomyomata may increase in size during estrogen use.
 6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.
 7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.
 8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.
 9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.
 10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.
 11. The lowest effective dose appropriate for the specific indication should be utilized. Studies of the addition of a progestin for 7 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10 to 13 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks which may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The choice of progestin and dosage may be important in minimizing these adverse effects.
 12. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen:
 - a. Increased sulfobromophthalein retention.
 - b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
 - c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
 - d. Impaired glucose tolerance.
 - e. Decreased pregnanediol excretion.
 - f. Reduced response to metyrapone test.
 - g. Reduced serum folate concentration.
 - h. Increased serum triglyceride and phospholipid concentration.
- B. *Information for patients:* See text which appears after PHYSICIAN REFERENCES.
- C. *Pregnancy Category X* – See Contraindications and Boxed Warning.
- D. *Nursing Mothers.* As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS

(See Warnings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

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|---------------------------------|-----------------------|
| 1. <i>Genitourinary system.</i> | Erythema multiforme. |
| Breakthrough bleeding, | Erythema nodosum. |
| spotting, change in | Hemorrhagic eruption. |
| menstrual flow. | Loss of scalp hair. |
| Dysmenorrhea. | Hirsutism. |

- Premenstrual-like syndrome.
- Amenorrhea during and after treatment.
- Increase in size of uterine fibromyomata.
- Vaginal candidiasis.
- Change in cervical eversion and in degree of cervical secretion.
- Cystitis-like syndrome.
- 2. *Breasts.*
Tenderness, enlargement, secretion.
- 3. *Gastrointestinal.*
Nausea, vomiting.
Abdominal cramps, bloating.
Cholestatic jaundice.
- 4. *Skin.*
Chloasma or melasma which may persist when drug is discontinued.
- 5. *Eyes.*
Steepening of corneal curvature.
Intolerance to contact lenses.
- 6. *CNS.*
Headache, migraine, dizziness.
Mental depression.
Chorea.
- 7. *Miscellaneous.*
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

ACUTE OVERDOSAGE

Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

1. *Given cyclically for short term use only:*

For treatment of moderate to severe *vasomotor symptoms, atrophic vaginitis* or *kraurosis vulvae* associated with the menopause.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., 3 weeks on and 1 week off).

Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

USUAL DOSAGE RANGES:

Vasomotor symptoms — 1.25 mg daily. If the patient has not menstruated within the last 2 months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding.

Atrophic vaginitis and kraurosis vulvae — 0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

2. *Given cyclically:* Female hypogonadism; female castration; primary ovarian failure.

USUAL DOSAGE RANGES:

Female hypogonadism — 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with Menest (esterified estrogens tablets), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last 5 days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure — 1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

3. *Given chronically:* Inoperable progressing prostatic cancer — 1.25 to 2.5 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women. (See INDICATIONS AND USAGE) — Suggested dosage is 10 mg three times daily for a period of at least 3 months.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

Tablets:

- 0.3 mg yellow, film-coated oblong tablet imprinted with M72 100's: NDC 61570-072-01
- 0.625 mg orange, film-coated oblong tablet imprinted with M73 100's: NDC 61570-073-01
- 1.25 mg green, film-coated oblong tablet imprinted with M74 100's: NDC 61570-074-01
- 2.5 mg pink, film-coated oblong tablet imprinted with M75 50's: NDC 61570-075-50

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PATIENT INFORMATION

WHAT YOU SHOULD KNOW ABOUT ESTROGENS

Estrogens are female hormones produced by the ovaries. The ovaries make several different kinds of estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we know, all these estrogens have similar properties and therefore much the same usefulness, side effects, and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved in their use, and how to use them as safely as possible.

This leaflet includes the most important information about estrogens, but not all the information. If you want to know more, you can ask your doctor or pharmacist to let you read the package insert prepared for the doctor.

USES OF ESTROGEN

Estrogens are prescribed by doctors for a number of purposes, including:

1. To provide estrogen during a period of adjustment when a woman's ovaries no longer produce it, in order to prevent certain uncomfortable symptoms of estrogen deficiency. (All women normally stop producing estrogens, generally between the ages of 45 and 55; this is called the menopause.)
2. To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically before the natural menopause.
3. To prevent pregnancy. (Estrogens are given along with a progestagen, another female hormone; these combinations are called oral contraceptives or birth control pills. Patient labeling is available to women taking oral contraceptives, and they will not be discussed in this leaflet.)
4. To treat certain cancers in women and men.

THERE IS NO PROPER USE OF ESTROGENS IN A PREGNANT WOMAN.

ESTROGENS IN THE MENOPAUSE

In the natural course of their lives, all women eventually experience a decrease in estrogen production. This usually occurs between ages 45 and 55, but may occur earlier or later. Sometimes the ovaries may need to be removed before natural menopause by an operation, producing a "surgical menopause."

When the amount of estrogen in the blood begins to decrease, many women may develop typical symptoms: Feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating throughout the body (called "hot flashes" or "hot flushes"). These symptoms are sometimes very uncomfortable. A few women eventually develop changes in the vagina (called "atrophic vaginitis") which cause discomfort, especially during and after intercourse.

Estrogens can be prescribed to treat these symptoms of the menopause. It is estimated that considerably more than half of all women undergoing the menopause have only mild symptoms or no symptoms at all and therefore do not need estrogens. Other women may need estrogens for a few months, while their bodies adjust to lower estrogen levels. Sometimes the need will be for periods longer than 6 months. In an attempt to avoid overstimulation of the uterus (womb), estrogens are usually given cyclically during each month of use, that is 3 weeks of pills followed by 1 week without pills.

Sometimes women experience nervous symptoms or depression during menopause. There is no evidence that estrogens are effective for such symptoms and they should not be used to treat them, although other treatments may be needed.

You may have heard that taking estrogens for long periods (years) after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence that this is so, however, and such long-term treatment carries important risks.

THE DANGERS OF ESTROGENS

1. *Cancer of the uterus.* If estrogens are used in the post-menopausal period for more than a year, there is an increased risk of *endometrial cancer* (cancer of the uterus). Women taking estrogens have roughly 5 to 10 times as great a chance of getting this cancer as women who take no estrogens. To put this another way, while a post-menopausal woman not taking estrogens has 1 chance in 1,000 each year of getting cancer of the uterus, a woman taking estrogens has 5 to 10 chances in 1,000 each year. For this reason *it is important to take estrogens only when you really need them.*

The risk of this cancer is greater the longer estrogens are used and also seems to be greater when larger doses are taken. For this reason *it is important to take the lowest dose of estrogen that will control symptoms and to take it only as long as it is needed.* If estrogens are needed for longer periods of time, your doctor will want to re-evaluate your need for estrogens at least every 6 months.

Women using estrogens should report any irregular vaginal bleeding to their doctors; such bleeding may be of no importance, but it can be an early warning of cancer of the uterus. If you have undiagnosed vaginal bleeding, you should not use estrogens until a diagnosis is made and you are certain there is no cancer of the uterus. If you have had your uterus completely removed (total hysterectomy) there is no danger of developing cancer of the uterus.

2. *Other possible cancers.* Estrogens can cause development of other tumors in animals, such as tumors of the breast, cervix, vagina, or liver, when given for a long time. At present there is no good evidence that women using estrogen in the menopause have an increased risk of such tumors, but there is no way yet to be sure they do not; and one study raises the possibility that use of estrogens in the menopause may increase risk of breast cancer many years later. This is a further reason to use estrogens only when clearly needed. While you are taking estrogens, it is important that you go to your doctor at least once a year for a physical examination. Also, if members of your family have had breast cancer or if you have breast nodules or abnormal mammograms (breast x-rays), your doctor may wish to carry out more frequent examinations of your breasts.
3. *Gall bladder disease.* Women who use estrogens after menopause are more likely to develop gall bladder disease needing surgery than women who do not use estrogens. Birth control pills have a similar effect.
4. *Abnormal blood clotting.* Oral contraceptives increase the risk of blood clotting in various parts of the body. This can result in a stroke (if the clot is in the brain), a heart attack (clot in a blood vessel of the heart), or a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal.

At this time use of estrogens in the menopause is not known to cause such blood clotting, but this has not been fully studied and there could still prove to be such a risk. It is recommended that if you have had clotting in the legs or lungs or a heart attack or stroke while you were using estrogens or birth control pills, you should not

use estrogens (unless they are being used to treat cancer of the breast or prostate). If you have had a stroke or heart attack or if you have angina pectoris, estrogens should be used with great caution and only if clearly needed (for example, if you have severe symptoms of the menopause).

SPECIAL WARNING ABOUT PREGNANCY

You should not receive estrogen if you are pregnant. If this should occur there is a greater than usual chance that the developing child will be born with a birth defect, although the possibility remains fairly small. A female child may have an increased risk of developing cancer of the vagina or cervix later in life (in the teens or twenties). Every possible effort should be made to avoid exposure to estrogens during pregnancy. If exposure occurs, see your doctor.

OTHER EFFECTS OF ESTROGENS

In addition to the serious known risks of estrogens described above, estrogens have the following side effects and potential risks:

1. *Nausea and vomiting.* The most common side effect of estrogen therapy is nausea. Vomiting is less common.
2. *Effects on breasts.* Estrogens may cause breast tenderness or enlargement and may cause the breasts to secrete a liquid. These effects are not dangerous.
3. *Effects on the uterus.* Estrogens may cause benign fibroid tumors of the uterus to get larger. Some women will have menstrual bleeding when estrogens are stopped. But if the bleeding occurs on days you are still taking estrogens you should report this to your doctor.
4. *Effects on liver.* Women taking oral contraceptives develop on rare occasions a tumor of the liver which can rupture and bleed into the abdomen. So far, these tumors have not been reported in women using estrogens in the menopause, but you should report any swelling or unusual pain or tenderness in the abdomen to your doctor immediately.

Women with a past history of jaundice (yellowing of the skin and white parts of the eyes) may get jaundice again during estrogen use. If this occurs, stop taking estrogen and see your doctor.

5. *Other effects.* Estrogens may cause excess fluid to be retained in the body. This may make some conditions worse, such as epilepsy, migraine, heart disease, or kidney disease.

SUMMARY

Estrogens have important uses, but they have serious risks as well. You must decide, with your doctor, whether the risks are acceptable to you in view of the benefits of treatment. Except where your doctor has prescribed estrogens for use in special cases of cancer of the breast or prostate, you should not use estrogens if you have cancer of the breast or uterus, are pregnant, have undiagnosed abnormal vaginal bleeding, clotting in the legs or lungs, or have had a stroke, heart attack or angina, or clotting in the legs or lungs in the past while you were taking estrogens. You can use estrogens as safely as possible by understanding that your doctor will require regular physical examinations while you are taking them and will try to discontinue the drug as soon as possible and use the smallest dose possible. Be alert for signs of trouble including:

1. Abnormal bleeding from the vagina.
2. Pains in the calves or chest or sudden shortness of breath, or coughing blood (indicating possible clots in the legs, heart, or lungs).
3. Severe headache, dizziness, faintness, or changes in vision (indicating possible developing clots in the brain or eye).
4. Breast lumps (you should ask your doctor how to examine your own breasts).
5. Jaundice (yellowing of the skin).
6. Mental depression.

Based on his or her assessment of your medical needs, your doctor has prescribed this drug for you. Do not give the drug to anyone else.

Rx only.



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