

High Folate Hikes Odds of Twinning After IVF

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Contributing Writer

A high plasma folate level around the time of conception raises the chance of twinning after in vitro fertilization, but not the chance of having a successful pregnancy, reported Paul Haggarty, Ph.D., of the Rowett Research Institute, Aberdeen, Scotland, and his associates.

“Our results suggest that the high inci-

dence of twin births associated with treatment for infertility could be reduced, while maintaining [live birth] rates, by encouraging women not to exceed recommended doses of folic acid and by identifying those at high risk of twins after double-embryo transfer on the basis of their plasma folate concentrations and age,” they wrote (*Lancet* 2006;367:1513-9).

“The need to increase the intake of folic acid to reduce the incidence of neural tube defects is not in doubt, but the associated

risks of multiple births after IVF need to be addressed,” they noted.

High folate levels have been associated with an increase in natural twinning, and “there are good biological reasons to suspect that B-vitamin exposure” also affects twinning in IVF pregnancies. Dr. Haggarty and his associates assessed vitamin B intake, plasma and red cell levels of folate, and six variants in genes known to be involved with B-vitamin metabolism in 602 women undergoing IVF. For comparison,

they also performed the same genetic analysis in 932 women who had conceived naturally and had singleton pregnancies.

Folate and vitamin B intake correlated with plasma and red-cell levels of folate. Neither one was associated with the rate of live births or the rate of pregnancy loss after IVF. However, both were associated with an increased rate of twinning in the IVF group.

Younger maternal age also was associated with an increased rate of twinning.

Women in the United Kingdom who are trying to conceive either naturally or through IVF are advised to take 400 mcg of supplementary folic acid daily before and after conception, to reduce the risk of neural tube defects. But flour and other

foods are not fortified with folate in the United Kingdom as they are in the United States. If they were, the average daily intake of folate would increase another 200 mcg in the United Kingdom, which would translate into an additional 600 IVF twin births there every year, the researchers said.

This is consistent with the 11%-13% increase in the rate of multiple births after IVF that was observed in the United States when folic acid fortification was mandated by the Food and Drug Administration in 1998, Dr. Haggarty and his associates added.

In an editorial comment accompanying this report, Dr. Gary Steinman of the department of ob.gyn. at Albert Einstein College of Medicine, New York, said that the mechanism underlying this association between folate and twinning still remains to be explained.

It may involve serum levels of insulin-like growth factor (IGF). Cows that have been crossbred to enhance their spontaneous twinning rate show twice the average serum levels of IGF, and human vegans—whose IGF levels typically are 13% lower than those in the general population—have a twinning rate that is comparably lower than the rate in vegetarians and omnivores, he said (*Lancet* 2006;367:1461-2).

Studies in ethnic populations also support an association between diet, serum IGF level, and twinning. The Yoruba women living in rural Nigeria have an unusually high twinning rate that is attributed to their high consumption of yams, which significantly raises their serum IGF levels. When they move to the city and change their diets, their IGF levels drop significantly, as does their twinning rate. Similarly, Japanese women have one of the lowest twinning rates of any ethnic group, but when they relocate to the United States and change their diets, their serum IGF rises dramatically and their twinning rate doubles, Dr. Steinman noted. ■

Loestrin® 24 Fe

(norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets) Ferrous fumarate tablets are not USP for dissolution and assay.

BRIEF SUMMARY—SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebrovascular or coronary artery disease (current or history)
- Valvular heart disease with thrombotic complications
- Severe hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast or personal history of breast cancer
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas or carcinomas, or active liver disease
- Known or suspected pregnancy
- Hypersensitivity to any component of this product

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited thrombophilias, hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks. The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older, with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in women aged 35 and nonsmokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in WARNINGS). Such increases in risk factors have been associated with an increased risk of heart disease and the risk increases with the number of risk factors present. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breastfeed.

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risk of cerebrovascular events (thrombotic and hemorrhagic strokes) although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for non-smokers users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for non-smokers users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias, hyperlipidemias, and obesity. Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which is judged appropriate for the individual patient.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persisted for at least 3 years for women 40 to 49 years old who had used oral contraceptives for five or more years but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages.

These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risk. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risk may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective and meets the individual patient needs.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. Although the risk of breast cancer may be slightly increased among current users of oral contraceptives (RR = 1.24), this excess risk decreases over time after oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use, and no relationships have been found with dose or type of steroid. The pattern of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small. Breast cancers diagnosed in current or previous oral contraceptive users tend to be less advanced clinically than in never-users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, these results are controversial about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast cancer and cervical cancers, a cause-and-effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although their occurrence is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; or proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy (see CONTRAINDICATIONS section).

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have little or no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1.a. and 1.d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users (see CONTRAINDICATIONS section).

9. ELEVATED BLOOD PRESSURE

Women with significant hypertension should not be started on hormonal contraceptives. An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see CONTRAINDICATIONS section). For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause (see WARNINGS 1.e.).

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. If bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem.

Absence of a withdrawal bleed may also occur. In the event of amenorrhea for two cycles or more, pregnancy should be ruled out. In the clinical trial with Loestrin 24 Fe, 31.4% of the women using Loestrin 24 Fe did not have a withdrawal menses in at least one of 6 cycles of use.

Some women may experience post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

PRECAUTIONS

1. SEXUALLY TRANSMITTED DISEASES

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

2. PHYSICAL EXAMINATION AND FOLLOW-UP

A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

3. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See WARNINGS 1.e.).

4. LIVER FUNCTION

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

5. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

6. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related.

7. CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

8. DRUG INTERACTIONS

Changes in contraceptive effectiveness associated with co-administration of other products:

a. Anti-infective agents and anticonvulsants

Co-administration of oral contraceptives with antibiotics increases the risk of contraceptive failure. Oral contraceptives containing ethinyl estradiol, norgestrel, and norethindrone may be co-administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin.

b. Anti-HIV protease inhibitors

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with co-administration of anti-HIV protease inhibitors. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

c. Herbal products

Herbal products containing St. John's Wort (*Hypericum perforatum*) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in plasma levels of estradiol associated with co-administered drugs:

Co-administration of atorvastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs:

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of tenazepam,

and diazepam have been reported with co-administration of combination oral contraceptives. Decreased plasma levels of theophylline have been reported with co-administration of combination oral contraceptives.

9. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

- Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 by radioimmunoassay, Free T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 concentration is unaltered.
- Other binding proteins may be elevated in serum.
- Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
- Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
- Glucose tolerance may be decreased.
- Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance in women who are pregnant shortly after discontinuing oral contraceptives.

10. CARCINOGENESIS

See WARNINGS section.

11. PREGNANCY

Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections.

12. NURSING MOTHERS

Small amounts of oral contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

13. PEDIATRIC USE

Safety and efficacy of Loestrin 24 Fe have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 years and in users age 16 years and older. Use of this product before menarche is not indicated.

14. GERIATRIC USE

This product has not been studied in women over 65 years of age and is not indicated in this population.

ADVERSE REACTIONS

The most common adverse events reported by 2 - 6% of the 743 women using Loestrin 24 Fe were, in order of decreasing incidence: Headache • Vaginal candidiasis • Upper respiratory infection • Nausea • Menstrual cramps • Breast tenderness • Sinusitis • Vaginitis (bacterial) • Abnormal cervical smear • Acne • Urinary tract infection • Mood swings • Weight gain • Vomiting • Metrorrhagia.

Among the 743 women using Loestrin 24 Fe, 46 women (6.2%) withdrew because of an adverse event. Adverse events occurring in 3% or more subjects leading to discontinuation of treatment were, in decreasing order: Abnormal bleeding (0.9%) • Nausea (0.8%) • Menstrual cramps (0.4%) • Increased blood pressure (0.4%) • Irregular bleeding (0.4%).

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section): Thrombophlebitis • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Cerebral thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives: Mesenteric thrombosis • Retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal pain, cramps, and bloating) • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema/fluid retention • Melasma/chloasma, which may persist • Breast changes (tenderness, pain, enlargement, and secretion) • Change in weight or appetite (increase or decrease) • Change in cervical ectropion and secretion • Possible diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine headache • Rash (allergic) • Temporary infertility after discontinuation of treatment • Edema/fluid retention • Melasma/chloasma, which may persist • Breast changes (tenderness, pain, enlargement, and secretion) • Change in weight or appetite (increase or decrease) • Change in cervical ectropion and secretion • Possible diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine headache • Rash (allergic) • Mood changes, including depression • Vaginitis, including candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses • Decrease in serum folate levels • Exacerbation of systemic lupus erythematosus • Exacerbation of porphyria • Exacerbation of chorea • Aggravation of varicose veins • Anaphylactoid/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.

The following adverse reactions have been reported in users of oral contraceptives, and a causal association has been neither confirmed nor refuted: Acne • Bud-Chari syndrome • Cataracts • Colitis • Changes in libido • Cystitis-like syndrome • Dizziness • Dysmenorrhea • Erythema multiforme • Erythema nodosum • Headache • Hemorrhagic eruption • Hemolytic uremic syndrome • Hirsutism • Impaired renal function • Loss of scalp hair • Nervousness • Optic neuritis, which may lead to partial or complete loss of vision • Pancreatitis • Premenstrual syndrome.

OVERDOSAGE

Serious effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.



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