

Immediate Postabortion IUD Not Problematic

VITALS

Major Finding: Immediate IUD placement after first-trimester abortion did not differ significantly from delayed placement in most complications.

Data Source: A multicenter randomized trial in 575 women.

Disclosures: The study was supported by an anonymous foundation. Dr. Bednarek disclosed having served on an advisory board for Bayer, maker of Mirena.

BY PATRICE WENDLING

ATLANTA — Immediate IUD placement following first-trimester abortion did not increase complications, and led to higher IUD utilization and lower repeat unintended pregnancy rates in a multicenter randomized trial in 575 women.

Patient-reported bleeding was

increased in the first 14 days among 199 women who had the levonorgestrel intrauterine system (LNG-IUS) (Mirena) inserted 15 minutes after suction aspiration, compared with 178 women who underwent insertion 2-6 weeks after aspiration.

The bleeding pattern, however, crossed over at days 14-21, when the majority of women in the delayed arm had their IUD placed, said Dr. Paula Bednarek, an ob.gyn. at the Oregon Health and Science

University in Portland.

During the first month after aspiration, the median number of bleeding days was 9 in the immediate group and 6.5 in the delayed group, which was statistically significant ($P = .0008$), but spotting was similar at a median of 8 days in both groups. There were no significant differences in either bleeding or spotting at 3 and 6 months' follow-up, Dr. Bednarek said at the annual meeting of the American Society for Reproductive Medicine.

Bleeding and spotting followed a similar pattern among an additional 107 women who chose a copper T380A IUD and were randomized to either immediate or delayed insertion, she said.

In all, 91 women randomized to delayed insertion did not receive an IUD.

When the investigators compared outcomes based on IUD type, the median number of bleeding days was similar during the first month, but greater

No significant differences were found in either bleeding or spotting at 3 and 6 months' follow-up after first-trimester abortion in the immediate and delayed-placement groups.

with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

Probable Dementia: In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to daily CE (0.625 mg) or placebo. In the WHIMS estrogen-alone ancillary study, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent nCI, 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years. In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent nCI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent nCI, 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women.

Gallbladder Disease: A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia: Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities: Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

Addition of a Progestin When a Woman Has Not Had a Hysterectomy: Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

Elevated Blood Pressure: In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

Hypertriglyceridemia: In women with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

Hepatic Impairment and/or Past History of Cholestatic Jaundice: Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

Hypothyroidism: Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention: Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia: Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

Exacerbation of Endometriosis: A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Exacerbation of Other Conditions: Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

Local Abrasion: A few cases of local abrasion induced by the Vagifem® applicator have been reported, especially in women with severely atrophic vaginal mucosa.

Laboratory Tests: Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

Drug-Laboratory Test Interactions: Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin

substrate, alpha-1-antitrypsin, ceruloplasmin). Increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS: The following serious adverse reactions are discussed elsewhere in the labeling: Cardiovascular Disorders [see Boxed Warning, Warnings and Precautions]; Endometrial Cancer [see Boxed Warning, Warnings and Precautions].

Clinical Study Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a 12-month randomized, double-blind, parallel group, placebo-controlled study, a total of 309 postmenopausal women were randomized to receive either placebo or Vagifem® 10 mcg tablets. Adverse events with an incidence of ≥5% in the Vagifem® 10 mcg group and greater than those reported in the placebo group are listed in Table 1.

Table 1: Treatment-Emergent Adverse Events Reported at a Frequency of ≥5% and More Frequent in Women Receiving Vagifem® 10 mcg

Body System Adverse Event	Treatment Number (%) of Women	
	Placebo N = 103 n (%)	Vagifem® N = 205 n (%)
Body As A Whole		
Back Pain	2 (2)	14 (7)
Digestive System		
Diarrhea	0	11 (5)
Urogenital System		
Vulvovaginal Mycotic Infection	3 (3)	17 (8)
Vulvovaginal Pruritis	2 (2)	16 (8)

N = Total number of women in study. n = Number of women who experienced adverse event.

In a 12-week, randomized, double-blind, placebo-controlled study, 138 postmenopausal women were randomized to receive either placebo or Vagifem® 25 mcg tablets. Adverse events with an incidence of ≥5% in the Vagifem® 25 mcg group and greater than those reported in the placebo group are listed in Table 2.

Table 2: Treatment-Emergent Adverse Events Reported at a Frequency of ≥5% and More Frequent in Women Receiving Vagifem® 25 mcg

Body System Adverse Event	Treatment Number (%) of Women	
	Placebo N = 47 n (%)	Vagifem® N = 91 n (%)
Body As A Whole		
Headache	3 (6)	8 (9)
Abdominal Pain	2 (4)	6 (7)
Back Pain	3 (6)	6 (7)
Respiratory System		
Upper Respiratory Tract Infection	2 (4)	5 (5)
Urogenital System		
Moniliasis Genital	1 (2)	5 (5)

N = Total number of women in study. n = Number of women who experienced adverse event.

Postmarketing Experience: The following adverse reactions have been reported during post approval use of Vagifem® 25 mcg. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System: Endometrial cancer, endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration

Breast: Breast cancer

Cardiovascular: Deep vein thrombosis

Gastrointestinal: Diarrhea

Skin: Urticaria, erythematous/pruritic rash, genital pruritis

Central Nervous System: Aggravated migraine, depression, insomnia

Miscellaneous: Fluid retention, weight increase, drug ineffectiveness, hypersensitivity, blood estrogen increase. Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

OVERDOSAGE: Overdosage of estrogen may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding in women. Treatment of overdose consists of discontinuation of Vagifem® together with institution of appropriate symptomatic care.

More detailed information is available upon request.

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