

# Medicaid to Pay Home-Birth Midwives in N.M.

BY ROBERT FINN  
San Francisco Bureau

New Mexico obstetricians are crying foul over an agreement forged by the state's human services department, several managed care organizations, and the state's midwives that will allow for Medicaid reimbursement for home births yet not require the midwives to carry liability insurance.

New Mexico has unusual parity in its numbers of midwives and obstetricians. According to the state Department of Health, there are 55 licensed midwives and 144 certified nurse-midwives in the state, a total of 199. According to the American College of Obstetricians and Gynecologists, there are 146 ACOG members (plus 51 junior fellows) in the state. In 1997, the New Mexico Medicaid program was privatized, and it's now run by managed care organizations (MCOs). The state requires that MCOs carry medical malpractice insurance, and MCOs in turn require the same of all their providers.

Midwives performing home births typically do not carry malpractice insurance. When that insurance is available, the cost is prohibitive, but few insurance companies are willing to write policies covering home births at any cost. It's not that there have been a large number of expensive claims, said Roberta Moore, maternal health program manager for the New Mexico Department of Health. Insurers simply don't see this market as profitable.

The new agreement provides for reimbursement of midwives provided that Medicaid-eligible women who choose to use their services acknowledge that they are aware of the midwife's lack of insurance and formally waive their rights to pursue legal action against the state,

the MCOs, or the midwife. The relatively small number of obstetricians in New Mexico and the state's rural character helped proponents of the agreement argue that it offers women in underserved remote areas access to care that they ordinarily would not have.

Dr. Sharon T. Phelan, professor of obstetrics and gynecology at the University of New Mexico, Albuquerque, doesn't buy this argument. In an interview, she noted that family physicians frequently perform births in rural areas of New Mexico where there are no obstetricians, so these areas are not really underserved. Those family physicians have mandatory malpractice insurance.

In addition, the agreement does not limit Medicaid reimbursement to midwives in rural areas. An Albuquerque-based midwife would receive reimbursement, even though there are many obstetricians in that city, Dr. Phelan pointed out.

Furthermore, there is a fundamental unfairness in allowing midwives to go without malpractice insurance while receiving about the same fee as an obstetrician does for a birth, Dr. Phelan said.

"When you're getting paid \$1,200 for 9 months of care and a delivery, there are places where docs are having to deliver a hundred babies just to meet their malpractice [insurance premiums]," Dr. Phelan said, noting that with premiums of approximately \$80,000 annually, New Mexico obstetricians are getting somewhat of a bargain, compared with colleagues in other parts of the country. New Mexico authorities basically treated the malpractice insurance problem "with an aspirin, which is to say [that midwives] are an exception to the rule and they don't have to carry insurance and they could still get paid. But they did not deal with the underlying problem," which

## Licensing Requirements in New Mexico

To be licensed as a direct-entry midwife in New Mexico, an applicant must complete 12 months of theoretical and clinical education at an accredited midwifery school, pass a licensing exam, and show evidence of the following clinical experience:

- ▶ Observing and managing 40 labors.
- ▶ Delivering 25 newborns and placentas.
- ▶ Completing 25 well-women health assessments.
- ▶ Making 100 prenatal visits with at least 15 different women.
- ▶ Starting one successful intravenous line.
- ▶ Performing 30 newborn examinations.
- ▶ Administering 15 uses of prophylactic eye medications.
- ▶ Making 30 postpartum visits with mothers and babies within 36 hours of deliveries.

▶ Collecting blood from 15 newborns for metabolic screening.

▶ Performing 15 6-week postpartum and/or yearly physical exams and Pap smears.

▶ Making 30 family planning visits, consultations, and/or referrals.

▶ Observing one neonatal-intensive-care nursery.

▶ Observing one high-risk obstetric care case.

▶ Providing one complete series of prepared childbirth classes.

▶ Observing one complete breastfeeding information series.

These requirements apply to direct-entry midwives only; certified nurse-midwives are registered nurses with additional certification from the American College of Nurse-Midwives after 2 years of advanced training.

Source: New Mexico Department of Health

is the malpractice insurance crisis.

And she noted that when a home birth starts going wrong, mother and baby would be transferred to a hospital. Supposing the infant or the mother dies or the child has an ongoing deficit, "who's going to be sued?" Dr. Phelan asked. "It's the doctor who inherited a problem that was already in development, because he or she is the one with the malpractice insurance. We're the ones with the deep pockets, so we're the ones who are going to get dragged to court and have to spend days in depositions and in court going through all that emotional stuff on our own."

The Midwives Alliance of North America (MANA), one of the two national midwifery associations (the other is the American College of Nurse-Midwives), said that

it's true that midwives aren't sued very often, but the reasons are unclear. According to Diane Holzer, MANA's president and a licensed midwife, part of the reason may be that patients are more satisfied with their care or that midwives are able to develop more of a personal connection with their clients.

She noted that even in the nine states in which Medicaid reimbursement for home births technically is permitted, many midwives cannot actually receive reimbursement. California, for example, allows for Medi-Cal reimbursement of home births only if the licensed midwife is being supervised by a physician. But according to Ms. Holzer, not a single physician in California is willing to supervise midwives.

Continued on following page

## Midwife Classifications Defined

A **Certified Midwife (CM)** is an individual educated in the discipline of midwifery who possesses evidence of certification according to the requirements of the American College of Nurse-Midwives. This term also is used in certain states as a designation of certification by the state or midwifery organization.

A **Certified Professional Midwife (CPM)** is a knowledgeable, skilled, and professional independent midwifery practitioner who has met the standards for certification set by the North American Registry of Midwives and is qualified to provide the midwifery model of care. The CPM is the only international credential that requires knowledge about and experience in out-of-hospital settings. CMs and CNMs typically practice in hospitals or clinics.

A **Certified Nurse-Midwife (CNM)** is an individual educated in the two disciplines of nursing and midwifery, who possesses evidence of certification according to the requirements of the American College of Nurse-Midwives. Unlike CMs or CPMs, CNMs are licensed in all 50 states.

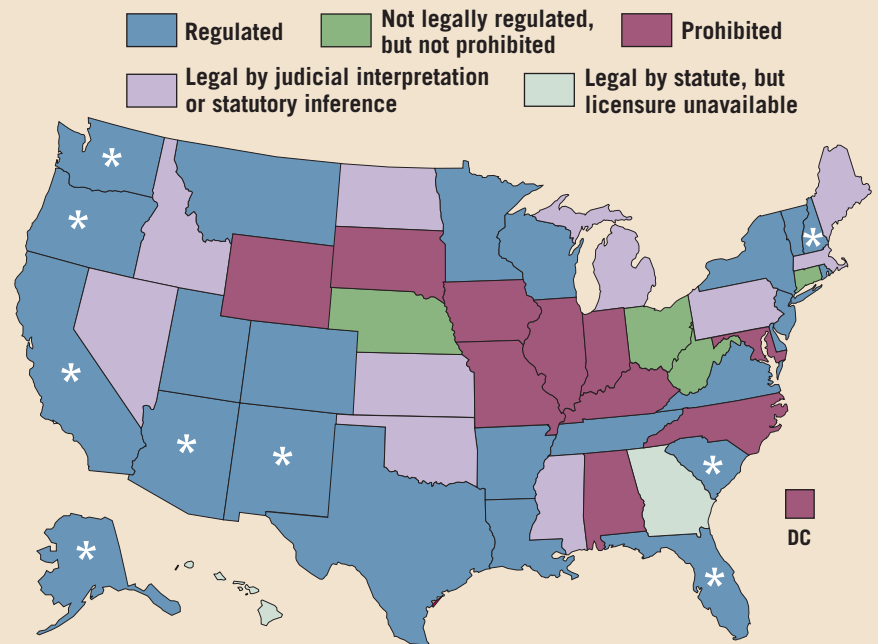
A **Direct-Entry Midwife (DEM)** is an independent practitioner educated in the discipline of midwifery through self-study, apprenticeship, a midwifery school, or a college- or university-based program distinct from the discipline of nursing. A direct-entry midwife typically provides care to healthy women and newborns throughout the childbearing cycle, primarily in out-of-hospital settings.

The term **Lay Midwife** is used to designate an uncertified or unlicensed midwife who was educated through informal routes such as self-study or apprenticeship rather than through a formal program. Other similar terms to describe uncertified or unlicensed midwives are **traditional midwife**, **traditional birth attendant**, **granny midwife**, and **independent midwife**.

A **Licensed Midwife (LM)** is a midwife who is licensed to practice in a particular jurisdiction (usually a state or province).

Sources: Midwives Alliance of North America; American College of Nurse-Midwives

## Regulation of Direct-Entry Midwives in the United States



\*These states have Medicaid reimbursement for midwives.

Note: A direct-entry midwife is an independent practitioner educated in the discipline of midwifery distinct from the discipline of nursing.

Source: April 2006 data, Midwives Alliance of North America

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Why is that? "It's the question of the ages," Ms. Holzer said in an interview. "The doctors all say it's a legal liability. They don't believe [home birth] is safe. But there are lots of studies out there that show that it is safe. I don't think that safety is the question if you take a look at the data out there. A lot of physicians have told us that their insurance companies have actually come out and said that if they back up out-of-hospital practitioners, they will be dropped."

Physicians tend to be more accepting of nurse-midwives than of those without

nursing degrees, Dr. Phelan said, adding that she has worked alongside nurse-midwives for 30 years, has helped train them, and is highly supportive of the use of nurse-midwives in birthing centers and hospitals. Some physicians may have the impression that someone can call herself a midwife after attending a 2-day workshop and participating in a handful of births. In reality, the requirements are more stringent. (See box, previous page.)

Despite the malpractice crisis that is causing many physicians to move away from obstetrics, the number of home births nationwide appears to be holding steady, Ms. Holzer said. "Birth is a natural

process, and doesn't need to be interfered with to the extent that it has become in this country," she added.

"I understand the reason why some women want home births," Dr. Phelan said. "There is the perception of the rigidity of hospital settings, the unwillingness to have family in attendance, [the concern that] we're going to cut episiotomies, the higher rate of C-section, all of those kinds of things. But I think much of that has changed. ... I think more and more hospitals are trying to have a more homelike birth experience with the ability to still provide the current technology and safety." ■

# Research Rule On Informed Consent Eyed

BY ELIZABETH MEHCATIE  
Senior Writer

ROCKVILLE, MD. — The Food and Drug Administration is reviewing a decade-old regulation that allows clinical studies of emergency treatments to be conducted without obtaining informed consent in people with certain life-threatening conditions.

The FDA's reappraisal and proposed revision of the rule were prompted by concerns that current safeguards do not provide enough protection of human subjects, and by comments that the safeguards are too onerous and impede important research.

At present, a narrow exception to the informed consent requirement exists in the case of patients who cannot provide consent because of their conditions and who have no family members available to give consent.

To be exempt from informed consent, an investigation must meet certain criteria, including the following:

- ▶ The patient is in a life-threatening situation.
- ▶ The available treatments are unproven or not satisfactory.
- ▶ Evidence supports the prospect of direct benefit to the individual.

Since the regulation went into effect in October 1996, the FDA has received 56 requests to conduct emergency research under this rule. A total of 21 studies have been conducted, are being conducted, or are about to start enrollment, according to the FDA.

The FDA has issued draft guidance geared toward institutional review boards, clinical investigators, and sponsors developing and conducting emergency research. The agency also sponsored a public hearing in October on emergency research.

At that hearing, presenters offered examples of emergency research that could not otherwise have been done without the exception.

Although the current rules could be simplified, the exception to informed consent is critical, said Dr. Paul Pepe, professor of surgery, medicine, and public health, and Riggs Family Chair in emergency medicine at the University of Texas Southwestern Medical Center at Dallas.

"Studies of the automated external defibrillator are an example of the tremendous lifesaving potential of emergency treatments," he said. Such studies can also show that treatments that have been widely accepted and appear to be logical may in fact be harmful in some populations, he added. For example, intravenous fluid resuscitation was found to be harmful in certain trauma populations. If these studies had not been done, Dr. Pepe explained, many people would have died.

The FDA will review written comments on the guidance, as well as comments made at the hearing, to determine whether the rule should be modified. ■

## ANGELIQ® TABLETS (Drospirenone and Estradiol) 0.5mg/1mg

### BRIEF SUMMARY OF PRESCRIBING INFORMATION

(for full prescribing information and patient information, please visit our website at www.angeliq-us.com)

#### Rx only

#### WARNING

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **WARNINGS, Cardiovascular disorders and Dementia**.) The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies and WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer**). The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens alone and during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use**.) Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials, and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

#### INDICATIONS AND USAGE

ANGELIQ is indicated in women who have a uterus for the: 1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

#### CONTRAINDICATIONS

Progestogens/estrogens should not be used in individuals with any of the following conditions: 1. Undiagnosed abnormal genital bleeding. 2. Known, suspected, or history of cancer of the breast. 3. Known or suspected estrogen-dependent neoplasia. 4. Active deep vein thrombosis, pulmonary embolism or history of these conditions. 5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction). 6. Renal insufficiency. 7. Liver dysfunction or disease. 8. Adrenal insufficiency. 9. ANGELIQ should not be used in patients with known hypersensitivity to its ingredients. 10. Known or suspected pregnancy. There is no indication for ANGELIQ in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

#### WARNINGS

ANGELIQ contains 0.5 mg of the progestin drospirenone that has antiandrogenic activity, including the potential for hyperkalemia in high-risk patients.

ANGELIQ should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal insufficiency, hepatic dysfunction, and adrenal insufficiency).

Use caution when prescribing ANGELIQ to women who regularly take other medications that can increase potassium, such as NSAIDs, potassium-sparing diuretics, potassium supplements, ACE inhibitors, angiotensin-II receptor antagonists, and heparin. Consider checking serum potassium levels during the first treatment cycle in high-risk patients.

#### See BOXED WARNINGS.

**1. Cardiovascular disorders** Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately. Risk factors for cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

**a. Coronary heart disease and stroke** In the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and strokes has been observed in women receiving oral CE compared to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies sections**.)

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 21 per 10,000 person-years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA-0.625mg/2.5mg per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years.

Two thousand three hundred and twenty-one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated 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 men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

**b. Venous thromboembolism (VTE)** In the Women's Health Initiative study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. (See **CLINICAL PHARMACOLOGY and Clinical Studies sections**.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

#### 2. Malignant neoplasms

**a. Endometrial cancer** The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

**b. Breast cancer** The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA

(see **CLINICAL PHARMACOLOGY, Clinical Studies**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration. The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 woman-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 woman-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, and risk factors, and prior mammogram results.

**3. Dementia** In the estrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, 2,947 hysterectomized women aged 65 to 79 years were randomized to CE or placebo. In the estrogen plus progestin WHIMS substudy, 4,532 postmenopausal women aged 65 to 79 years were randomized to CE/MPA or placebo.

In the estrogen alone substudy, 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 estrogen alone versus placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for estrogen alone versus placebo was 37 versus 25 cases per 10,000 woman-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies and PRECAUTIONS, Geriatric Use**.)

After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 - 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 woman-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 woman-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies and PRECAUTIONS, Geriatric Use**.)

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

**5. Hypercalcemia** Estrogen administration may lead to severe hypercalcemia in patients 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.

**6. Visual abnormalities** Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is 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.

#### PRECAUTIONS

##### A. GENERAL

##### 1. A general 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 a possible increased risk of breast cancer.

**2. 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 estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

**3. Hypertriglyceridemia** In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

**4. Impaired liver function and past history of cholestatic jaundice** Estrogens may be poorly metabolized in patients with impaired liver function. For patients 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.

The clearance of drospirenone was decreased in patients with moderate hepatic impairment.

**5. Hypothyroidism** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients 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. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

**6. Fluid retention** Because estrogen and estrogen/progestin therapy may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

**7. Hypocalcemia** Estrogens should be used with caution in individuals with severe hypocalcemia.

**8. Hyponatremia** As an aldosterone antagonist, drospirenone may increase the possibility of hyponatremia in high-risk patients.

**9. Ovarian cancer** The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 - 3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 woman-years. In some epidemiologic studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

**10. Exacerbation of endometriosis** Endometriosis may be exacerbated with administration of estrogens.

**11. Exacerbation of other conditions** Estrogens 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.

**B. PATIENT INFORMATION** Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe ANGELIQ.

**C. LABORATORY TESTS** Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).

#### D. DRUG/LABORATORY TEST INTERACTIONS

1. 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 anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. 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. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG)) leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, and increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

#### E. CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS and PRECAUTIONS**.) Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNINGS, CONTRAINDICATIONS, and WARNINGS sections**.)

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.24 to 10.3 times the exposure (AUC of drospirenone) of women taking a 1 mg dose, there was an increase in carcinomas of the hardener gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 2.3 to 51.2 times the exposure of women taking a 1 mg dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. (See **WARNINGS section**.)

**F. PREGNANCY** ANGELIQ should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

**G. NURSING MOTHERS** Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when ANGELIQ is administered to a nursing woman.

After administration of an oral contraceptive containing drospirenone about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mg drospirenone in an infant.

#### H. PEDIATRIC USE

ANGELIQ is not indicated in children.

**I. GERIATRIC USE** There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing ANGELIQ to determine whether those over 65 years of age differ from younger subjects in their response to ANGELIQ.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 92% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (89%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women who were older than 70. (See **WARNINGS, Dementia**.)

#### ADVERSE REACTIONS

##### See BOXED WARNINGS, WARNINGS, AND PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials 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. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. The following are adverse events reported with ANGELIQ occurring in >5% of subjects:

Table 4. Adverse Events Regardless of Drug Relationship Reported at a Frequency of >5% in a 1-year Double-blind Clinical Trial

ADVERSE EVENT	E2 1 MG (N=226) n (%)	ANGELIQ (N=227) n (%)
<b>BODY AS A WHOLE</b>		
Abdominal pain	29 (12.8)	25 (11)
Pain in extremity	15 (6.6)	19 (8.4)
Back pain	11 (4.9)	16 (7)
Flu syndrome	15 (6.6)	16 (7)
Accidental injury	15 (6.6)	13 (5.7)
Abdomen enlarged	17 (7.5)	16 (7)
Surgery	6 (2.7)	12 (5.3)
<b>METABOLIC &amp; NUTRITIONAL DISORDERS</b>		
Peripheral edema	12 (5.3)	4 (1.8)
<b>NERVOUS SYSTEM</b>		
Headache	26 (11.5)	22 (9.7)
<b>RESPIRATORY SYSTEM</b>		
Upper respiratory infection	40 (17.7)	43 (18.9)
Sinusitis	8 (3.5)	12 (5.3)
<b>SKIN AND APPENDAGES</b>		
Breast pain	34 (15.0)	43 (18.9)
<b>UROGENITAL</b>		
Vaginal hemorrhage	43 (19.0)	21 (9.3)
Endometrial disorder	22 (9.7)	4 (1.8)
Leukorrhea	14 (6.2)	3 (1.3)

The following additional adverse reactions have been reported with estrogen and/or estrogen/progestin therapy:

- 1. Genitourinary system** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, dysmenorrhea, increase in size of uterine leiomyomata, vaginitis, including vaginal candidiasis, change in amount of cervical secretion, changes in cervical ectropion, ovarian cancer, endometrial hyperplasia, endometrial cancer.
- 2. Breasts** Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.
- 3. Cardiovascular** Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.
- 4. Gastrointestinal** Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, increase in incidence of gall bladder disease, pancreatitis, enlargement of hepatic hemangiomas.
- 5. Skin** Chloasma or melasma, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, pruritus, rash.
- 6. Eyes** Retinal vascular thrombosis, intolerance to contact lenses.
- 7. Central nervous system** Headache, migraine, dizziness, mental depression, chorea, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia.
- 8. Miscellaneous** Increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, anaphylactoid/anaphylactic reactions including urticaria and angioedema, hypocalcemia, exacerbation of asthma, increased triglycerides.

#### OVERDOSE

In cases of ANGELIQ overdose, monitor serum concentrations of potassium and sodium since drospirenone has antiminerocorticoid properties.

Serious ill effects have not been reported following acute ingestion of large doses of progestin/estrogen-containing oral contraceptives by young children. Overdose may cause nausea and withdrawal bleeding may occur in females.

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