Legro RS, Zaino RJ, Demers LM, et al. The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome. Am J Obstet Gynecol. 2007;196:402.e1–e11.

Q. Is rosiglitazone superior to metformin for women with PCOS?

A. Maybe. Rosiglitazone outperformed metformin in this small sample of obese women with polycystic ovary syndrome (PCOS). On average, it improved unbound testosterone, 2-hour glucose and 2-hour insulin levels, and the daily urinary progestin-to-estrogen ratio. Ovulation increased on both drugs, alone and in combination, but 5 of 16 women showed no evidence of ovulation after 6 months.

EXPERT COMMENTARY

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Metformin may take as long as 6 months to exert an optimal effect on ovulation, and rosiglitazone 3 to 4 months to improve insulin sensitivity

Insulin resistance is central to the anovulation and hyperandrogenism of many women with PCOS, and insulin-sensitizing drugs are increasingly used for chronic treatment, especially to ameliorate the metabolic sequelae of type 2 diabetes and cardiovascular disease. In the diabetes world, combining insulin-sensitizing drugs of different classes yields superior results, compared with monotherapy.

On this basis, Legro and colleagues conducted a pilot study to compare the effects of metformin and rosiglitazone, alone and in combination, on ovulation, androgens, and endometrial histology in women with PCOS. Women were randomized to metformin or rosiglitazone monotherapy for 12 weeks, followed by 12 weeks of combination therapy.

Researchers used urinary pregnanediol-3-glucuronide to detect ovulation, and did periodic endometrial biopsies.

Duration of study was insufficient

Metformin may take as long as 6 months to exert an optimal effect on ovulation, and thiazolidinediones (including rosiglitazone) may require 3 to 4 months to improve insulin sensitivity. Therefore, neither drug was given for a sufficient duration to assess its individual effects.

In this study, the number of subjects was small (5 women completed the metformin arm, and 9 women the rosiglitazone arm), and the groups differed greatly at baseline, with the metformin group being heavier and the rosiglitazone group being more hirsute and having higher serum testosterone and insulin levels. These baseline differences make comparison of the 2 groups after 3 months of monotherapy difficult, because the seeming improvements in testosterone and insulin in the rosiglitazone group may have been due to regression to the mean rather than a true effect of the drug.

Both drugs improved ovulation. Combining the 2 drugs did not add further benefit, but lack of benefit may have been the result of the brief duration of combined therapy (12 weeks).

Both drugs tended to normalize endometrial histology in the women who had simple hyperplasia at baseline. The number of women was small, but the finding is buttressed by 2 earlier studies in PCOS showing that metformin improves uterine vascularity and circulating glycodelin, a marker of endometrial function.[1,2]

No change to clinical practice—yet

As a pilot study, the trial was not meant to change clinical practice—nor should it.

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The future trial resulting from this pilot study should incorporate longer durations of treatment and yield more answers.

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Q. HT and breast cancer: Does the type of progestin matter?

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2007; Feb 27 [epub ahead of print].

A. Yes. In this study from France, the association between estrogen–progestin regimens and breast cancer varied significantly, depending on the progestin. The relative risk of invasive breast cancer was 1.08 for progesterone (95% confidence interval 0.89–1.31), 1.16 for dydrogesterone (0.94–1.43), and 1.69 for other progestins (1.50–1.91).

EXPERT COMMENTARY

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Fear of breast cancer discourages many women from using menopausal hormone therapy (HT), and fuels anxiety among patients and physicians alike. A large body of evidence from clinical trials and observational studies indicates that the use of estrogen-only therapy for less than 5 years has minimal, if any, impact on the risk of breast cancer.[1–5] In contrast, use of combination estrogen–progestin hormone therapy for more than 5 years is associated with an elevated risk of breast cancer,[3,6,7] and this risk is greater than the risk associated with the use of estrogen alone. This modestly increased risk is comparable to the elevated risk of breast cancer associated with lifestyle choices such as daily alcohol use, postmenopausal obesity, and lack of regular exercise.[8]

Few have focused on effects of specific progestins

Because the addition of a progestin to estrogen therapy in women with a uterus appears to play a key role in increasing the risk of breast cancer, and because a variety of progestins are available (including levonorgestrel, medroxyprogesterone acetate [MPA], norethindrone acetate, and progesterone), it makes sense to ask whether some progestins increase the risk of breast cancer more than others.

Although MPA is the most widely used progestin in menopausal practice in this country—and was the progestin used in the Women's Health Initiative (WHI) trial of combination HT—other progestins are more common in Europe. The evidence has not definitively demonstrated that the choice of progestin affects the degree of breast cancer risk in women using HT.[3]

Large French population had high rate of HT use

HT is commonly used by menopausal women in France, and progesterone is the most widely prescribed progestin for endometrial protection, as Fournier and colleagues note. They conducted this large, prospective cohort study to assess HT use and breast cancer risk in almost 100,000 French teachers and wives of teachers, with intriguing results. Among the women followed in this study, 70% had used HT. The mean age at initiation was 52.4 years, and the mean duration of use and follow-up was 7 and 8.1 years, respectively.

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The relative risk of invasive breast cancer was 1.08 for progesterone, 1.16 for dydrogesterone, and 1.69 for other progestins

Findings in regard to estrogen differ from those of other studies

Overall, the risk of being diagnosed with invasive breast cancer was significantly elevated with the use of estrogen alone, at a relative risk of 1.29 (95% confidence interval 1.02–1.65). This small elevation contrasts the findings of the WHI and Nurses' Health studies, which identified no increased risk of breast cancer with estrogen alone.[4,5]

Transdermal estrogen is widely used in menopausal women in France; route of estrogen administration did not affect breast cancer risk in this study.

Progesterone was associated with no elevated risk

The use of combination HT with MPA or norethindrone acetate was associated with higher relative risks than estrogen alone: 1.48 (1.02–2.16) and 2.11 (1.56–2.86), respectively. In contrast, combination HT with progesterone was not associated with an elevated risk of breast cancer, with a relative risk of 1.08 (0.89–1.31).

Fournier and colleagues point out that theirs is the first epidemiologic study to assess the risk of breast cancer associated with HT containing progesterone. They also cite recent data in postmenopausal primates indicating that combination HT with micronized progesterone causes lower rates of proliferation in lobular and ductal breast epithelium, compared with MPA-based hormone therapy.[9]

Clinical recommendations: For now, simply ensure adequate progestin

The findings of a single study generally should not dictate clinical practice. It remains the standard of care to ensure sufficient progestin (whether levonorgestrel, MPA, norethindrone acetate, or micronized progesterone) to prevent endometrial hyperplasia when prescribing HT for menopausal women with a uterus.

The findings of this study raise the possibility that progesterone may be safer than other progestins with respect to breast neoplasia. Additional epidemiologic data assessing the safety of progesterone in comparison with other progestins are welcome, but studies would need to be conducted in regions like France, where progesterone is widely used.

In the meantime, ObGyns who wish to prescribe micronized progesterone as part of combination HT should rule out peanut allergy and advise patients to take the micronized tablets at bedtime because of their tendency to cause sleepiness. The appropriate dosage of micronized progesterone to prevent endometrial proliferation in menopausal women using estrogen is 100 mg nightly or 200 mg cyclically for 12 or more days each month.[10] ■

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Progesterone may be safer than other progestins with respect to breast neoplasia