Metformin for gestational diabetes: As safe and as effective as insulin?

YES In this open-label randomized trial comparing metformin, with or without supplemental insulin, with insulin alone, metformin did not increase the risk of perinatal complications and was preferred by a majority of women.

Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, for the MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003–2015.

EXPERT COMMENTARY

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FAST TRACK

Compared with insulin, metformin did not increase the risk of perinatal complications and was preferred by most women

Rowan and colleagues add to the data on the potential benefits of oral hypoglycemic agents, compared with insulin, in managing gestational diabetes. The presumption was that dietary treatment alone would not result in adequate glycemic control.

In the study, women assigned to metformin were given a starting dosage of 500 mg once or twice daily, which was then increased to a maximum daily dosage of 2,500 mg. According to the authors, women assigned to insulin were prescribed the drug "according to usual practice," although that practice was never defined. In addition, if adequate glycemic control was not achieved in the metformin group, insulin was added.

Overall, 363 of the women who received metformin completed the study, with 195 receiving metformin alone and 168 ultimately receiving metformin plus insulin. In the other arm, 370 of the women assigned to insulin completed the study. Maternal baseline characteristics were the same for both groups, except that a statistically greater number of patients in the metformin group had had three or more pregnancy terminations or miscarriages.

The primary outcome of this study was a composite of various neonatal outcomes. Of the variables analyzed, significant differences were found only for prematurity (delivery <37 weeks), which was greater in the metformin group, and neonatal hypoglycemia (any blood glucose level <28.8 mg/dL), which occurred more frequently in the insulin group.

A variety of secondary outcomes were also analyzed, with no meaningful differences. The authors conclude that metformin with or without supplemental insulin is "effective and safe" for women with gestational diabetes. In the next sentence, however, they observe that "follow-up data are needed to establish long-term safety."

WHAT THIS EVIDENCE MEANS FOR PRACTICE

All the attention to gestational diabetes has yet to significantly improve obstetric outcomes such as birth injury, C-section, or serious short-term neonatal morbidity. Nor is it any surprise that women in this study preferred metformin to insulin; most people would prefer a pill to a "shot." However, nearly half of the pill group ended up needing a shot anyway.

Metformin is pregnancy category B and should not be used by nursing women. Rowan and colleagues acknowledge that long-term safety data are insufficient to recommend the use of oral hypoglycemic agents to manage diabetes in pregnancy.

This trial was well designed and executed, but insulin remains, in my opinion, the standard of care. Oral hypoglycemic agents just are not "ready for prime time" when it comes to gestational diabetes.

›› JOHN T. REPKE, MD

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Do aromatase inhibitors extend disease-free survival after tamoxifen therapy in breast cancer survivors?

YES In postmenopausal women treated for early-stage hormone receptor-positive breast cancer who have completed therapy with tamoxifen, treatment with the aromatase inhibitors letrozole or exemestane increased disease-free survival.

Muss HB, Tu D, Ingle JN, et al. Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG Intergroup Trial MA.17. J Clin Oncol. 2008;26:1956–1964.

Goss PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol. 2008;26:1948–1955.

Mamounas EP, Jeong J-H, Wickerham DL, et al. Benefits from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention to treat analysis of the National Surgical Adjuvant Breast and Bowel Project B-33 Trial. J Clin Oncol. 2008;26:1965–1971.

EXPERT COMMENTARY
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Survival clearly improves in postmenopausal women with early-stage receptor-positive breast cancer who take tamoxifen or an aromatase inhibitor for 5 years after treatment. The risk of recurrence remains heightened, however, for many years after adjuvant endocrine therapy ends. These three studies explore the effects of extended hormonal adjuvant therapy in women who have completed tamoxifen therapy.

Canadian trial focused on letrozole

In the first trial, known as MA.17 and sponsored by the National Cancer Institute of Canada, more than 5,000 women who had

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How do you code when using letrozole as adjuvant breast Ca therapy?

At the moment, there is no adequate way to capture data on the many women who receive long-term pharmacotherapy to prevent a recurrence of estrogen receptor-positive breast cancer: The recommended code, **V58.69** (long-term [current] use of other medications), does not help you identify the type of treatment.

That dilemma will be resolved on October 1, however, when three new codes are added:

- **V07.51** Prophylactic use of selective estrogen-receptor modulators (SERMs)
- **V07.52** Prophylactic use of inhibitors
- **V07.59** Prophylactic use of agents affecting estrogen receptors and estrogen levels.

When using the new codes, you should report a secondary code that identifies the patient's:

- status as estrogen receptor-positive **(V86.0)**
- family history of breast cancer, if any **(V16.3)**
- genetic susceptibility to cancer **(V84.01–V84.09)**
- personal history of breast cancer **(V10.3)**
- postmenopausal status **(V49.81)**.

In addition, the new V07.5 series of codes may also be used with neoplasm codes if the patient is still in active treatment for cancer.

An "includes" note with each of these codes indicates the most typical drugs that would be reported. For example: SERMs include raloxifene, tamoxifen, and toremifene; aromatase inhibitors include anastrozole, exemestane, and letrozole; and drugs that act on estrogen receptors and estrogen levels include such estrogen-receptor down-regulators as fulvestrant, gonadotropin-releasing hormones, the agonist goserelin, leuprolide, and megestrol.

›› MELANIE WITT, RN, CPC-OGS, MS

taken tamoxifen for 5 years were randomized to letrozole or placebo. At a median follow-up of 30 months, letrozole significantly increased disease-free survival.

This study analyzed the risks and benefits of letrozole by age group:

- younger than 60 years
- 60 to 69 years
- 70 years and older.

After 4 years of letrozole, disease-free survival increased to a similar degree in all groups, but achieved statistical significance in the youngest group.

Compared with placebo, the youngest women experienced a lower incidence of vaginal bleeding and a greater incidence of arthralgias. Women in the 60-to-69-year group experienced more insomnia, hot flushes, arthralgias, and alopecia. In contrast, women 70 years or older had a side effect profile that was similar to that of the placebo group.

Both treated women and those randomized to placebo had a similar rate of diagnosis of new osteoporosis or fracture. One reason for this finding may be enhanced bone density from the 5 years of tamoxifen that preceded letrozole.

Letrozole is effective even long after tamoxifen therapy has ended

The study by Goss and colleagues explored the use of letrozole among women originally assigned to the placebo group in the MA.17 trial. After that trial was unblinded, roughly 66% of placebo-assigned women opted for open-label use of letrozole. The median time since completion of 5 years of tamoxifen therapy among these women was 2.8 years.

Although women who chose not to take letrozole had a lower baseline risk of disease recurrence, women who *did* choose letrozole had greater disease-free survival at a median follow-up of 5.3 years (hazard ratio, 0.39; *P*=.004), demonstrating that letrozole is effective even when it is not initiated for several years after discontinuation of tamoxifen.

Exemestane also improved survival

The National Surgical Adjuvant Breast and Bowel Project (NSABP), funded by the US National Cancer Institute, randomized postmenopausal women to exemestane or placebo. All women had receptor-positive breast cancer and had taken tamoxifen for 5 years. When the MA.17 trial was unblinded, accrual to the NSABP was halted, and all women randomized to placebo were offered exemestane. At a median follow-up of 30 months, disease-free survival improved marginally (*P*=.07) in the 560 women originally assigned to exemestane, compared with the 344 women originally randomized to placebo.

An editorial accompanying these studies describes trials still under way to assess the benefits and risks of aromatase inhibitors beyond 5 years of therapy.[1] The findings of those trials will help determine whether extended use is beneficial.

Reference

1. Lin NU, Winer EP. Optimizing endocrine therapy for estrogen receptor-positive breast cancer: treating the right patients for the right length of time. J Clin Oncol. 2008; 26:1919–1921.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Overall, these three studies demonstrate that the extension of adjuvant endocrine therapy beyond the initial 5 years (in tamoxifen users) improves disease-free survival without impairing quality of life or causing major toxicity. Younger postmenopausal women are more likely than older women to experience menopausal symptoms when taking an aromatase inhibitor.

To prevent fractures, assess bone mineral density at baseline and prescribe bisphosphonates when necessary.

The good news? Aromatase inhibitors are easily tolerated in most women. Significant arthralgias or other bothersome side effects in some subgroups, however, may make it necessary to weigh the benefits of aromatase inhibitors against quality of life.

›› ANDREW M. KAUNITZ, MD

FAST TRACK

In women who had early-stage, hormone-receptor-positive breast cancer and who had taken tamoxifen for 5 years, an aromatase inhibitor increased disease-free survival