Cochrane for Clinicians

Putting Evidence into Practice

Levonorgestrel-Releasing Intrauterine System for Reducing Heavy Menstrual Bleeding

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Clinical Question

Is the levonorgestrel-releasing intrauterine system (Mirena) safe and effective for reducing heavy menstrual bleeding?

Evidence-Based Answer

The levonorgestrel-releasing intrauterine system is more effective than other medical therapies at reducing menstrual bleeding volume (mean difference [MD] = 67 mL; 95% CI, 43 to 91 mL), with similar rates of adverse effects. The effectiveness of the levonorgestrel-releasing intrauterine system compared with endometrial ablation and hysterectomy has been inadequately studied.[1] (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Heavy menstrual bleeding is defined by the perception of excessive bleeding affecting a patient's quality of life and is common among those of reproductive age. Numerous medical and surgical therapeutic options exist for heavy menstrual bleeding. The authors of this Cochrane review sought to evaluate the effectiveness and safety of the levonorgestrel-releasing intrauterine system compared with other therapeutic options for heavy menstrual bleeding.[1]

This Cochrane review included 25 randomized controlled trials and 2,511 patients, with studies comparing the levonorgestrel-releasing intrauterine system with no treatment, placebo, medical therapies (including nonsteroidal anti-inflammatory drugs, antifibrinolytic drugs, and hormone-containing medications), endometrial ablation, and hysterectomy.[1] Participants were of reproductive age with regular heavy periods. The study locations and durations were heterogeneous, spanning multiple countries and ranging in length from three months to 10 years. The primary outcomes were effectiveness (reduction in blood loss measured objectively, semi-objectively, or subjectively) and patient satisfaction (measured on a five-point Likert scale). Secondary outcomes were quality of life, adverse effects, withdrawal from treatment, treatment failure, need for subsequent surgery, and cost.

The levonorgestrel-releasing intrauterine system consistently reduced heavy menstrual bleeding compared with other medical therapies. The intrauterine system was associated with greater reduction of bleeding volume from baseline compared with an oral contraceptive measured by objective methods (MD = 67 mL; 95% CI, 43 to 91 mL; two studies; 170 women) and a separate analysis of semi-objective methods (MD = 55 mL; 95% CI, 28 to 82 mL; three studies; 335 women; duration of six to 12 months). Most of the remaining six randomized controlled trials also noted reduction in heavy menstrual bleeding volume with the levonorgestrel-releasing intrauterine system compared with other medical therapies, although treatment outcomes could not be pooled because of clinical heterogeneity.

Bleeding outcomes were mixed when comparing the levonorgestrel-releasing intrauterine system and endometrial ablation, with two studies showing improvement of bleeding with endometrial ablation, two showing improvement with the levonorgestrel-releasing intrauterine system, and four with no clear difference. Data were insufficient to compare the effectiveness between the levonorgestrel-releasing intrauterine system and hysterectomy.

The authors note that the quality of all studies was limited by low participant numbers, and confidence in the findings was also low. The levonorgestrel-releasing intrauterine system caused similar rates of adverse effects and lower rates of treatment failure compared with

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other medical therapies. The intrauterine system had higher treatment failure rates and more adverse effects, especially progestin-related effects, including mastalgia, weight gain, and acne, compared with endometrial ablation. The authors were unable to adequately compare the levonorgestrel-releasing intrauterine system and hysterectomy.

These findings reflect conclusions of previous reviews demonstrating that the levonorgestrel-releasing intrauterine system is likely the most effective medical therapy for heavy menstrual bleeding.[2] The National Institute for Health and Care Excellence guidelines for heavy menstrual bleeding recommend considering the levonorgestrel-releasing intrauterine system as first-line treatment for patients with heavy menstrual bleeding with no identified pathology.[3]

The practice recommendations in this activity are available at http://www.cochrane.org/CD002126.

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Can Pioglitazone Prevent or Delay Type 2 Diabetes in Patients with Prediabetes?

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Clinical Question

How does pioglitazone (Actos) compare with other pharmacologic glucose-lowering agents and lifestyle interventions in the prevention or delay of type 2 diabetes mellitus in individuals with prediabetes?

Evidence-Based Answer

Pioglitazone prevents or delays the incidence of type 2 diabetes in individuals with prediabetes when compared with placebo (absolute risk reduction [ARR] = 11.3%; 95% CI, 0.9% to 15.6%; number needed to treat [NNT] = 9) or no intervention (ARR = 13.3%; 95% CI, 11.6% to 14.9%; NNT = 7). Compared with metformin, however, pioglitazone does not reduce the incidence of type 2 diabetes in those with prediabetes.[1] (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Prediabetes is a condition with various definitions describing patients whose average blood glucose levels are higher than normal.[1] Approximately 34.5% of the U.S. adult population has prediabetes, with a higher prevalence in men and a similar prevalence among all ethnic groups.[2] The authors of this review sought to determine the effect of pioglitazone (a thiazolidinedione) on the prevention or delay of type 2 diabetes and its associated complications in individuals with prediabetes.

This review included 27 randomized controlled trials with 4,186 participants; most trials were conducted in outpatient settings, three of which were in the United States.[1] Primary outcomes of this review were all-cause mortality, incidence of type 2 diabetes, and serious adverse events. Most studies identified individuals with prediabetes using the World Health Organization 1999, American Diabetes Association (ADA) 2003, or ADA 2010 diagnostic criteria for impaired fasting glucose or impaired glucose tolerance. A range of 15 to 30 mg of pioglitazone and varied doses of metformin (38 mg, 250 mg, and 750 mg) were typically used. The length of interventions ranged from six to 36 months.

Pioglitazone was compared with metformin, acarbose (Precose), or repaglinide in three studies involving 331 participants. Each comparison group had matching behavior-changing interventions. All-cause mortality was not reported in the included studies, and there were no serious adverse events in the comparison groups. Pioglitazone did not reduce the incidence of type 2 diabetes compared with metformin (low-certainty evidence).

Compared with placebo, pioglitazone reduced or delayed type 2 diabetes (ARR = 11.3%; 95% CI, 0.9% to 15.6%; NNT = 9; six studies; n = 1,395; low-certainty evidence). However, this effect was no longer present in three studies after a washout and extended follow-up period ranging between three weeks and one year after the study period.

Compared with no intervention, pioglitazone performed better in the prevention or delay of type 2 diabetes (ARR = 13.3%; 95% CI, 11.6% to

14.9%; NNT = 7; 16 studies; n = 2,053; moderate-certainty evidence). Analysis of all-cause mortality revealed no harmful effects (three studies; n = 866; very low-certainty evidence) and no serious adverse events with the use of pioglitazone (seven studies; n = 1,211; low-certainty evidence).

Pioglitazone was compared with behavior-changing interventions (diet and exercise) in one study involving 96 participants. There was no significant effect on the incidence of type 2 diabetes or serious adverse events with the use of pioglitazone (downgraded to low-certainty evidence).

Limitations of this review include variations in the diagnostic criteria for prediabetes, exclusion of individuals with comorbidities commonly encountered in primary care settings (except for hypertension), and differences in the dosages of administered medications.

The ADA recommends yearly testing of individuals who have prediabetes given the estimated annual rate of conversion from prediabetes to type 2 diabetes of 3% to 11%.[3,4] Current treatment recommendations for those with prediabetes include intensive behavioral lifestyle intervention (modeled after the Diabetes Prevention Program, a goal-based intervention to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity to at least 150 minutes per week), dietary modification, individualized medical nutrition therapy, and consideration of medications such as thiazolidinediones.[5] The cost of 30 tablets of 15-mg pioglitazone is about $15, and the cost of 60 tablets of 500-mg metformin is about $14.[6] Pioglitazone carries a black box warning for causing or worsening congestive heart failure.

The practice recommendations in this activity are available at http://www.cochrane.org/CD013516.

Editor's Note: The ARRs, CIs, and NNTs reported in this Cochrane for Clinicians were calculated by the author based on raw data provided in the original Cochrane review.

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