GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Is Elagolix with and/or without Add-Back Therapy Effective in Reducing Heavy Menstrual Bleeding in Pre-Menopausal Women with Fibroids?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids

Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med.* 2020; 382:328–340.

KEY TAKEAWAY: Elagolix, an oral GnRH antagonist, decreases heavy uterine bleeding in premenopausal women with uterine leiomyomas, alone or in conjunction with hormonal therapy, compared to placebo.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Uterine leiomyomas, also known as uterine fibroids, are benign neoplasms that respond to endogenous female hormones and can result in menorrhagia. Elagolix causes quick, but easily reversible down-regulation of these hormones. This mechanism is thought to have the ability to decrease abnormal uterine bleeding associated with fibroids via its antagonistic effects on GnRH.

PATIENTS: Pre-menopausal women with heavy uterine bleeding and uterine leiomyomas

INTERVENTION: Elagolix or elagolix + hormone supplementation

CONTROL: Placebo

OUTCOME: Menstrual blood loss <80 mL in the last month of the study; minimum of 50% decrease in menstrual blood loss compared to pre-treatment flow

METHODS (BRIEF DESCRIPTION):

- Two separate studies done with the same design (UF-1 and UF-2).
- Patients were randomized to elagolix 300 mg BID or placebo.
- Both evaluators and patients were blinded.
- UF-1 and UF-2 each comprised of a 2.5 to 3.5 month screening period.
- The two phase III trials were conducted for six months.
- An intervention group in UF-1 and UF-2 was provided "add-back therapy", hormonal supplementation with estradiol 1 mg and norethindrone acetate 0.5 mg, once daily.

INTERVENTION (# IN THE GROUP):

- Elagolix: 199 (UF-1=104; UF-2=95)
- Elagolix + add-back therapy: 395 (UF-1=206; UF-2=189)

COMPARISON (# IN THE GROUP): 196 (UF-1=102; UF-2=94)

FOLLOW UP PERIOD: 12 months

RESULTS:

- Elagolix alone significantly decreased the risk of heavy menstrual bleeding compared to placebo, with participants in the elagolix alone group more likely to meet the primary endpoint than those in the placebo group.
  - UF-1: Risk Ratio [RR] 9.7 (95% CI, 5.0–19)
  - UF-2: RR 7.1 (95% CI, 3.8–13)
- Elagolix plus add-back therapy significantly decreased the risk of heavy menstrual bleeding compared to placebo, with participants in the elagolix plus add-back therapy group more likely to meet the primary endpoint than those in the placebo group.
  - UF-1: RR 7.9 (95% CI, 4.1–16)
  - UF-2: RR 7.2 (95% CI, 3.9–14)
- Adverse Events:
  - UF-1 and UF-2 intervention groups experienced vasomotor symptoms, such as hot flashes.
  - The UF-1 intervention groups experienced intermenstrual bleeding, particularly in patients who received add-back therapy.
  - Elagolix alone caused loss of bone mineral density.

LIMITATIONS:

- Sponsored by AbbVie, the company that manufactures elagolix.
- Follow up period may not have been long enough to accurately assess the harms associated with this treatment.
- Dropout rates were 20% in UF-1 and 24% in UF-2.
- Missing final month blood loss data were imputed with multiple imputation.

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Physical Rehab after Hospitalization for Heart Failure: Strengthening the Evidence for Exercise

Physical Rehabilitation for Older Patients Hospitalized for Heart Failure

Kitzman DW, Whellan DJ, Duncan P, et al. Physical Rehabilitation for Older Patients Hospitalized for Heart Failure. *N Engl J Med*. 2021; 385(3): 203–216. doi:10.1056/NEJMoa2026141.

KEY TAKEAWAY: Early, tailored, and progressive rehabilitation improves physical function in older, frail adults hospitalized for acute decompensated heart failure.

STUDY DESIGN: Multicenter, single-blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Acute Decompensated Heart Failure (ADHF) is the leading cause of hospitalization among older adults in the US, often resulting in long term decline in physical function as well as high rates of readmission and death. Current guidelines do not address physical dysfunction in hospitalized patients for heart failure.

PATIENTS: Older adults hospitalized for ADHF

INTERVENTION: Early, transitional, tailored progressive physical rehabilitation program

CONTROL: Usual care as recommended by medical providers

OUTCOME: Physical function

Secondary Outcome: Rate of re-hospitalization for any cause at 6 months

METHODS (BRIEF DESCRIPTION):

- Patients were adults ≥60 years old admitted for ADHF.
- Randomization was stratified by ejection fraction and clinical site.
- Intervention was progressive physical rehabilitation program focusing on strength, mobility, balance, and endurance, consisting of 36 60-minute sessions over 12 weeks, followed by individualized exercise program at home.
- The control group (usual care) received a phone call every two weeks and had an in-person clinical visit at 1 month and 3 months after discharge. Usual care could include traditional PT or cardiac rehabilitation.
- Physical function was measured by the score on the Short Physical Performance Battery (SPPB) at 3 months.
  - SPPB includes a standing balance test, a gait-speed test, and a strength test, each scored 0–4, with a higher score indicating better physical function.
  - Minimum clinically important difference is 0.5.

INTERVENTION (# IN THE GROUP): 175

COMPARISON (# IN THE GROUP): 174

FOLLOW UP PERIOD: 6 months after hospitalization

RESULTS:

Primary Outcome –

- The mean SPPB score at 3 months was higher in the intervention group compared to the control group (8.3 vs 6.9; mean between-group difference 1.5; 95% CI, 0.9 to 2.0).

Secondary Outcome –

- No significant difference in the rate of re-hospitalization for any cause at 6 months between the intervention and control groups (RR 0.93; 95% CI, 0.66–1.2).

LIMITATIONS:

- Limited power to detect secondary outcomes.
- Benefits of the intervention over usual care may have been moderated by exercise therapy received by the control group.
- Patients were not blinded.
- Intervention was quite intensive and may not be available or feasible for all patients.

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Finding the Sweet Spot: Is There Benefit in Screening Earlier for Gestational Diabetes?

Early Gestational Diabetes Screening in Obese Women: A Randomized Controlled Trial

Harper LM, Jauk V, Longo S, Biggio JR, Szychowski JM, Tita AT. Early gestational diabetes screening in obese women: a randomized controlled trial. *Am J Obstet Gynecol*. 2020; 222(495):e1–8. doi: 10.1016/j.ajog.2019.12.021

KEY TAKEAWAY: Early screening between 14–20 weeks gestation for gestational diabetes (GDM) in pregnant women with BMI ≥30 does not result in a reduction in adverse maternal or neonatal outcomes compared with routine screening at 24–28 weeks.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: More than one-third of reproductive-age US women have BMI ≥30, which is associated with elevated risk of adverse pregnancy outcomes, including GDM. In 2013, ACOG suggested early GDM screening if BMI ≥30; however, USPSTF found insufficient evidence to recommend this. More evidence is needed to determine whether earlier GDM screening and treatment is associated with improved maternal and perinatal outcomes.

PATIENTS: Pregnant patients with BMI ≥30

INTERVENTION: Early GDM screening at 14–20 weeks' gestation

CONTROL: Routine GDM screening at 24–28 weeks' gestation

OUTCOME: Composite of fetal macrosomia (>4,000 g), cesarean delivery, hypertensive diseases of pregnancy, shoulder dystocia, neonatal hyperbilirubinemia, and neonatal hypoglycemia.

Secondary Outcomes: Individual outcomes above, gestational age (GA) at delivery, severity of hypertensive disease, large-for-gestational-age (LGA) status, and use of glucose-lowering medications.

METHODS (BRIEF DESCRIPTION):

- Included patients were pregnant less than 20 weeks GA with BMI ≥30 and receiving prenatal care at University of Alabama at Birmingham.
- Exclusion criteria included pre-existing DM, known fetal anomalies, prior cesarean delivery, history of bariatric surgery, other medical co-morbidities, and chronic steroid use.
- All patients received screening HbA1c at 14–20 weeks' gestation.
- Patients randomized to GDM screening at either 14–20 weeks or 24–28 weeks gestation, and randomization was stratified by BMI >40 and study site.
- Two-step GDM screening: One hour non-fasting 50 g glucose tolerance test (GTT) and, if abnormal, followed by three hour 100 g GTT.
- GDM diagnosis was based on Carpenter-Coustan criteria: Fasting ≥95 mg/dL, one hour ≥180 mg/dL, two hours ≥155 mg/dL, three hour ≥140 mg/dL
- If negative early screening, patients still received routine GDM screening at 24–28 weeks.
- Patients diagnosed with diabetes by A1c and/or three hour GTT were treated per standard of care.

INTERVENTION (# IN THE GROUP): 459

COMPARISON (# IN THE GROUP): 463

FOLLOW UP PERIOD: 6 weeks postpartum

RESULTS:

Primary Outcome –

- No difference between groups with the composite outcome (57% vs 51%; risk ratio [RR] 1.1; 95% CI, 0.99–1.3).

Secondary Outcomes –

- Individual components of the composite outcome did not vary significantly between groups.
- More patients in the early screening group received insulin versus the routine screening group (2.4% vs 0.7%; *P*=.03).
- Among patients diagnosed with GDM, patients in the early screening group had significantly earlier mean GA at delivery (36.7 ± 4.5 weeks vs 38 ± 1.7 weeks; *P*<.01).

LIMITATIONS:

- Lack of blinding of patients and providers.
- Use of composite as primary outcome; limited power to detect differences in individual maternal and perinatal outcomes.
- Only 83% in early screening group received early screening.
- Glucose control after diagnosis of GDM not assessed by study protocol.

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Does *H. pylori* Treatment Reduce the Risk of Gastric Cancer?

Family History of Gastric Cancer and *Helicobacter pylori* Treatment

Choi IJ, Kim CG, Lee JY, et al. Family History of Gastric Cancer and *Helicobacter pylori* Treatment. *N Engl J Med.* 2020; 382(5):427–436. doi:10.1056/NEJMoa1909666

KEY TAKEAWAY: *H. pylori* treatment reduces the risk of gastric cancer in patients with a first-degree family history of gastric cancer.

STUDY DESIGN: Single center, double blind, placebo controlled, randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: A family history of gastric cancer in first degree relatives is associated with a 2–3 times greater risk of gastric cancer. Previous studies have shown an association between *H. pylori* infection and gastric cancer. The American College of Gastroenterology clinical guideline has no recommendation regarding routine testing or treatment of *H. pylori* infection due to insufficient evidence. The International Agency for Research on Cancer has suggested further studies to investigate the utility of population based screening and treatment.

PATIENTS: Men and women 40–65 years old with confirmed *H. pylori* infection and at least one confirmed first degree relative with gastric cancer

INTERVENTION: Amoxicillin 1,000 mg + clarithromycin 500 mg + lansoprazole 30 mg BID for 7 days

CONTROL: Same number and duration of placebo pills

OUTCOME: Development of gastric cancer

Secondary Outcomes: Development of gastric cancer according to *H. pylori* eradication status

METHODS (BRIEF DESCRIPTION):

- Endoscopy was performed to confirm *H. pylori* infection and absence of coexisting disease.
- 1,838 eligible participants randomized for treatment or placebo, in 1:1 ratio stratified according to sex.
- After 162 participants were excluded, 832 received treatment and 844 placebo.
- Treatment was administered and adherence was monitored via telephone.
- Surveillance endoscopies were performed every two years. Biopsy specimens from suspicious lesions were evaluated for adenoma or carcinoma.
- Final endoscopy performed at end of trial. Biopsy specimens from antrum lesser, corpus lesser, and corpus greater curvatures and graded for gastritis and *H. pylori* infection.

INTERVENTION (# IN THE GROUP): 832

COMPARISON (# IN THE GROUP): 844

FOLLOW UP PERIOD: Median follow up 9.2 years for primary outcome & median follow up 10.2 years for secondary outcome

RESULTS:

Primary Outcome –

- The intervention resulted in a reduced risk of gastric cancer compared to the placebo group (1.2% vs 2.7% respectively; Hazard Ratio [HR] 0.45; 95% CI, 0.21–0.94; NNT=66).

Secondary Outcomes –

- The intervention group had an eradication of *H. pylori* infection of 70% compared to 7% of the placebo group.
- Persistent *H. pylori* increased the risk of developing gastric cancer compared to eradicated *H. pylori* (2.9% vs 0.8% respectively; HR 0.27; 95% CI, 0.10–0.7; NNT=48).

Conclusion –

- 55% lower relative risk in treatment vs placebo group.
- 73% lower relative risk in eradicated vs persistent infection.

LIMITATIONS:

- The study was performed at a single center in South Korea.
- Genetic susceptibility to gastric cancer and *H. pylori* virulence factors were not evaluated and may be risk factors for development.
- Ethical concerns regarding non-treatment of confirmed *H. pylori* in placebo group.

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