GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 5 - Issue 13

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of March 31- April 4, 2025

SPOTLIGHT:

Balloons Instead of Prostaglandins for Induction of Labor?

- Tirzepatide: A Game Changer for MASH Resolution and Fibrosis Management
- Early Diagnosis of Asthma and COPD: Helping Patients Feel Better?
- Droplets or Capsules: Minoxidil Route of Delivery for Male Pattern Hair Loss
- Bro, Do You Even Keto?

Balloons Instead of Prostaglandins for Induction of Labor?

Balloon Catheters vs Vaginal Prostagladins for Labor Induction (CPI Collaborative): An Individual Participant Data Meta-Analysis of Randomized Controlled Trials

Jones MN, Palmer KR, Pathirana MM, et al. Balloon catheters versus vaginal prostaglandins for labour induction (CPI Collaborative): an individual participant data meta-analysis of randomised controlled trials. *Lancet*. 2022;400(10364):1681-1692. doi:10.1016/S0140-6736(22)01845-1

KEY TAKEAWAY: Balloon catheters reduce the risk of adverse perinatal outcomes compared to vaginal prostaglandins, while both methods result in similar maternal outcomes and cesarean delivery rates.

STUDY DESIGN: Meta-analysis of 12 randomized controlled trials (N=5,460)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Previous meta-analyses comparing balloon catheters and vaginal prostaglandins for labor induction have indicated similar effectiveness between the two methods. However, these studies have been limited in their ability to draw definitive conclusions about the safety profiles of these approaches. To address these limitations and provide a more comprehensive evaluation of both effectiveness and safety, researchers conducted a new meta-analysis specifically comparing balloon catheters to vaginal prostaglandins in the context of labor induction.

PATIENTS: Women undergoing induction of labor

INTERVENTION: Balloon catheters

CONTROL: Vaginal prostaglandins (standard of care)

PRIMARY OUTCOME: Cesarean delivery rate, adverse perinatal outcomes, adverse maternal outcomes

METHODS (BRIEF DESCRIPTION):

- Included participants were pregnant women at or beyond 37-week gestation of a viable singleton pregnancy with an unripe cervix and a Bishop score of 4–6.
- Trials excluded pregnant women with multiple gestations and previous uterine surgery.
- The included studies utilized the following:
  - Cervical ripening methods other than balloon catheters or vaginal prostaglandins
  - Combination balloon catheters + prostaglandin E (PGE)
  - High dose (>50 mcg) prostaglandin E1 (PGE-1)
- Intention to treat analysis was utilized to assess primary outcome of caesarean deliveries and its indication, between balloon catheter induction compared vaginal prostaglandin induction.
- Adverse perinatal outcomes were defined as Apgar score <7 at five minutes, arterial umbilical cord pH <7.1, admission to neonatal intensive care unit (NICU), severe respiratory compromise, neonatal infection, neonatal death, or stillbirth.
- Adverse maternal outcomes were defined as admission to the intensive care unit (ICU), maternal infection, severe postpartum hemorrhage, or maternal death.

INTERVENTION (# IN THE GROUP): 2,663

- Single balloon catheters: 1,324
- Double balloon catheters: 1,339

COMPARISON (# IN THE GROUP): 2,797

- PGE-1: 462
- Prostaglanin E2 (PGE-2): 2,797

FOLLOW-UP PERIOD: End of hospital stay

RESULTS:

Primary Outcome –

- Balloon catheters were associated with a lower risk of adverse perinatal outcomes compared to vaginal prostaglandins (10 trials, n=4,452; odds ratio [OR] 0.80; 95% CI, 0.70–0.92).
- There was no significant difference in composite adverse maternal outcomes between balloon catheters and vaginal prostaglandins (10 trials, n=4,326; OR 1.0; 95% CI, 0.89–1.2).
- There was no significant difference in cesarean delivery rates between balloon catheters and vaginal prostaglandins (12 trials, n=5,414; OR 1.1; 95% CI, 0.96–1.2).

LIMITATIONS:

- Some eligible trials lacked individual participant data.
- Limited data were available for certain secondary outcomes.

- Most included trials had some risk of bias due to the inability to blind participants, but they were still considered methodologically robust.

Keshava Gali, MD
Community Health Care FMRP
Tacoma, WA

Tirzepatide: A Game Changer for MASH Resolution and Fibrosis Management

Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis

Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. *N Engl J Med*. 2024;391(4):299-310. doi:10.1056/NEJMoa2401943

KEY TAKEAWAY: Tirzepatide significantly improves metabolic dysfunction–associated steatohepatitis (MASH) resolution without worsening fibrosis.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: MASH is a progressive liver disease associated with increased risks of cardiovascular and liver-related complications. Weight reduction has been shown to improve MASH outcomes, but the efficacy of pharmacological interventions like tirzepatide remains under investigation. The objective of this study was to assess if tirzepatide could help resolve MASH without worsening liver fibrosis.

PATIENTS: Adults with MASH

INTERVENTION: Tirzepatide

CONTROL: Placebo

PRIMARY OUTCOME: Resolution of MASH without worsening of fibrosis

Secondary Outcome: Improvement of at least one fibrosis stage without worsening MASH

METHODS (BRIEF DESCRIPTION):

- Phase two, a multicenter, double-blind, randomized, placebo-controlled trial was conducted across 130 sites in 10 countries.
- Participants were mostly White (86%) or Asian (12%), with 36% identifying as Hispanic or Latino, between 18–80 years old, and 58% had type 2 diabetes.
- Inclusion criteria:
  - Biopsy-confirmed MASH
  - Fibrosis stage two (moderate) or three (severe)
  - BMI 27–50 kg/m²
  - Non-alcoholic fatty liver disease (NAFLD) activity score of ≥4
- Exclusion criteria included cirrhosis, evidence of hepatic decompensation, excessive alcohol consumption (>14 standard drinks per week for women and >21 standard drinks per week for men), uncontrolled diabetes (HbA1c >9.5%), and use of other weight loss medications.
- Participants were randomized in a 1:1:1:1 ratio to receive tirzepatide (5 mg, 10 mg, or 15 mg) or placebo, administered once weekly for 52 weeks.
- All participants received counseling on nutrition and physical activity as part of site-specific programs.
- Liver biopsies were performed at baseline and week 52 to assess the resolution of MASH and fibrosis progression.
- Biopsies were evaluated by central pathologists blinded to the trial-group assignments.
- The primary outcome assessed the resolution of MASH at week 52, defined as the absence of steatohepatitis (steatosis score of 0 or simple steatosis with an inflammation score of 0–1 and ballooning score of 0) without worsening fibrosis (no increase in fibrosis stage).
- The secondary outcomes assessed the improvement of at least one fibrosis stage, scored on a scale of zero (no fibrosis) to four (cirrhosis), at week 52 without worsening MASH.
- Logistic regression was used for binary outcomes.
  - Multiple imputation was applied to handle missing data.

INTERVENTION (# IN THE GROUP):

- 5 mg tirzepatide: 47
- 10 mg tirzepatide: 47
- 15 mg tirzepatide: 48

COMPARISON (# IN THE GROUP): 48

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Tirzepatide 5 mg improved MASH resolution without worsening fibrosis compared to placebo (risk difference [RD] 34%; 95% CI, 17–50).
- Tirzepatide 10 mg improved MASH resolution without worsening fibrosis compared to placebo (RD 46%; 95% CI, 29–62).
- Tirzepatide 15 mg improved MASH resolution without worsening fibrosis compared to placebo (RD 53%; 95% CI, 37–69).

Secondary Outcome –

- Tirzepatide 5 mg improved fibrosis by at least one stage without worsening MASH compared to placebo (RD 25%; 95% CI, 5–46).
- Tirzepatide 10 mg improved fibrosis by at least one stage without worsening MASH compared to placebo (RD 22%; 95% CI, 1–42).
- Tirzepatide 15 mg improved fibrosis by at least one stage without worsening MASH compared to placebo (RD 21%; 95% CI, 1–42).

LIMITATIONS:

- Short trial duration of 52 weeks
- The sample size was underpowered for some subgroup analyses.
- Underrepresentation of some demographic groups, including African and Indian populations

Sai Suseel Sarvepalli, MBBS
Central Michigan University FMRP
Saginaw, MI

Early Diagnosis of Asthma and COPD: Helping Patients Feel Better?

Early Diagnosis and Treatment of COPD and Asthma: A Randomized, Controlled Trial

Aaron SD, Vandemheen KL, Whitmore GA, et al. Early Diagnosis and Treatment of COPD and Asthma - A Randomized, Controlled Trial. *N Engl J Med*. 2024;390(22):2061-2073. doi:10.1056/NEJMoa2401389

KEY TAKEAWAY: Patients with respiratory symptoms evaluated by a pulmonologist and nurse educator have a lower rate of annualized health care utilization for respiratory illness compared to routine care.

STUDY DESIGN: Case-finding randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: Studies indicate that undiagnosed chronic obstructive pulmonary disease (COPD) and asthma lead to worse disease-specific and overall health outcomes when compared with healthy age-matched controls. The overall global health burden related to COPD and asthma is thus difficult to estimate. This study investigated whether early diagnosis and treatment of COPD and asthma improved overall health outcomes.

PATIENTS: Adults with respiratory symptoms

INTERVENTION: Specialty care

CONTROL: Usual care

PRIMARY OUTCOME: Healthcare utilization for respiratory illness

Secondary Outcome: Disease-specific quality of life, symptom burden

METHODS (BRIEF DESCRIPTION):

- This trial combined a case-finding study with a randomized controlled trial.
- Patients ≥18 years old within 90 minutes from one of 17 clinical trial sites were surveyed.
- Patients who had respiratory symptoms within the prior six months completed the Asthma Screening Questionnaire (ASQ). Scores range from 0–20, with higher scores indicating more respiratory symptoms. Individuals >60 years old with <6 on the ASQ also completed the COPD diagnostic questionnaire.
- Patients were excluded if a prior physician documented lung disease, they used respiratory inhalers (except for as needed short acting beta agonists (PRN SABA), or had contraindication to spirometry.
- At baseline, the intervention group had a mean age of 63 years old, 64% were male, and 52% had moderate airflow obstruction.
- The control group had an average age of 63 years old, 58% were male, and 43% had moderate airflow obstruction.
- The intervention group received evaluation and management by a trial pulmonologist and asthma/COPD educator on the day of randomization, at four months, and at a 12-month follow-up.
- The control group received the usual care from their primary care provider (PCP).
- The primary outcome was assessed via the annualized rate of participant-initiated health care utilization for respiratory illness by monthly telephone encounters.
- Secondary outcomes included:
  - Changes in disease-specific quality of life were assessed via the Saint George Respiratory Questionnaire (SGRQ). Scores range from 0–100, with lower scores indicating better health status.
  - Symptom burden was assessed using the COPD Assessment Test (CAT). Scores range from 0–40, with lower scores indicating better health status.
  - Both outcomes were assessed at six and 12 months

INTERVENTION (# IN THE GROUP): 253

COMPARISON (# IN THE GROUP): 253

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Patients in the treatment group had a lower annualized rate of participant health care utilization for respiratory illness as compared to usual care (0.53 vs 1.1 events per person year, respectively; incidence rate ratio [IRR] 0.48; 95% CI, 0.36–0.63).

Secondary Outcome –

- Patients in the intervention group had a greater improvement in disease-specific quality of life compared to usual care (mean difference [MD] –3.5 points; 95% CI, –6.0 to –0.9).
- Patients in the intervention group had a greater reduction in symptom burden at 12 months compared to usual care (MD –1.3 points; 95% CI, –2.4 to –0.1).

LIMITATIONS:

- The difference in the primary outcome was driven by mild respiratory illnesses (not hospitalizations or outpatient or emergency room visits).
- Participants were required to have an active phone number and were restricted to the Canadian healthcare system.
- There was an inefficient sampling method; 27,000 phone calls were made to identify 595 adults.
- Participants were unblinded.

Stuart Jones, MD
Alaska FMRP
Anchorage, AK

Droplets or Capsules: Minoxidil Route of Delivery for Male Pattern Hair Loss

Oral Minoxidal vs Topical Minoxidal for Male Androgenetic Alopecia: A Randomized Clinical Trial

Penha MA, Miot HA, Kasprzak M, Müller Ramos P. Oral Minoxidil vs Topical Minoxidil for Male Androgenetic Alopecia: A Randomized Clinical Trial. *JAMA Dermatol*. 2024;160(6):600-605. doi:10.1001/jamadermatol.2024.0284

KEY TAKEAWAY: Oral minoxidil is a safe, non-inferior alternative to topical minoxidil as a treatment for male androgenic alopecia (AGA).

STUDY DESIGN: Double-blind, single site, placebo-controlled randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and significant loss to follow-up)

BRIEF BACKGROUND INFORMATION: AGA is a common cause of hair loss among men, which can lead to decreased self-esteem and quality of life. Currently approved treatments include oral finasteride and topical minoxidil, both of which have associated adverse side effects. This study aimed to investigate oral minoxidil as a potential alternative treatment modality for AGA.

PATIENTS: Adult males with AGA

INTERVENTION: Oral minoxidal

CONTROL: Topical minoxidal

PRIMARY OUTCOME: Change in terminal hair densities in targeted areas

Secondary Outcome: Change in total hair densities in targeted areas, dermatologist consensus for clinical improvement, adverse effects, blood pressure, heart rate

METHODS (BRIEF DESCRIPTION):

- Men 18–55 years old with AGA were recruited from a single, specialized clinic in Brazil and randomized 1:1 in a blinded manner.
- Inclusion criteria included:
  - Diagnosis of AGA using the Norwood Hamilton scale. Scores range from 1–7, with increasing scores indicating increasing alopecia. A "V" pattern indicates hair loss at the vertex, and an "A" pattern indicates hair loss straight back without central sparing.
  - Diagnosis of AGA must be established by a board-certified dermatologist through clinical and trichoscopic assessment.
- Exclusion criteria included patients who underwent treatment for alopecia in the past six months, had a history of hair transplant, cardiopathy, nephropathy, dermatoses or other confounding conditions causing hair loss, or hypersensitivity to minoxidil.
- Participants had a mean age of 37 years old, most with Norwood-Hamilton 3V (53% in oral vs 60% in topical group) and an average systolic blood pressure of 122 mmHg.
- The treatment group received oral minoxidil 5 mg nightly and a placebo solution to apply 1 mL twice daily.
- The comparison group received topical minoxidil 5% solution to apply 1 mL twice daily and a matching placebo pill.
- The primary outcome was the change in terminal hair density in target areas over 24 weeks as measured by automated counting and confirmed by three dermatologists (frontal and vertex using photographs as well as two shaved circular 2 cm^2 areas leaving 1 mm-long hair shafts, terminal hair counted as hair with a diameter ≥0.06 mm).
- Secondary outcomes were measured via total hair density in target areas (total hair count in frontal and vertex areas), standardized clinical photographs, and adverse effects, blood pressure, and heart rate at 24 weeks.

INTERVENTION (# IN THE GROUP): 33

COMPARISON (# IN THE GROUP): 35

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- There was no significant difference in the mean change from baseline in terminal hair density for oral compared to topical minoxidil in the frontal or vertex regions.
  - Frontal region (3.1 hairs/cm^2; 95% CI, –18 to 22)
  - Vertex region (23 hairs/cm^2; 95% CI, –0.03 to 43)
- Oral minoxidil improved terminal hair density compared to topical minoxidil in the vertex region (27%; 95% CI, 6.5–48).

- Oral minoxidil did not significantly improve terminal hair density compared to topical minoxidil in the frontal region (13%; 95% CI, –12 to 38).

Secondary Outcome –

- There was no significant difference in total hair density between the two groups in the frontal or vertex areas.
- There was no significant difference in mean heart rate or blood pressure between the two groups.
- Oral minoxidil resulted in more frequent hypertrichosis compared to topical minoxidil (49% vs 25%, respectively; *P*=.02).
- Oral minoxidil resulted in more frequent headaches compared to topical minoxidil (14% vs 2%, respectively; *P*=.05).
- Topical minoxidil resulted in more frequent Scalp eczema compared to oral minoxidil (16% vs 2%, respectively; *P*=.02).

LIMITATIONS:

- The study was conducted at a single center in Brazil, limiting generalizability.
- The study had a small sample size.
- There was a high rate of loss to follow-up.

Eric Chan, MD
Alaska FMRP
Anchorage, AK

Bro, Do You Even Keto?

Mediterranean Diet vs Very Low-Calorie Ketogenic Diet: Effects of Reaching 5% Body Weight Loss of Body Composition in Subjects with Overweight and with Obesity-A Cohort Study

Di Rosa C, Lattanzi G, Spiezia C, et al. Mediterranean Diet versus Very Low-Calorie Ketogenic Diet: Effects of Reaching 5% Body Weight Loss on Body Composition in Subjects with Overweight and with Obesity-A Cohort Study. *Int J Environ Res Public Health*. 2022;19(20):13040. Published 2022 Oct 11. doi:10.3390/ijerph192013040

KEY TAKEAWAY: A very low-calorie ketogenic diet (VLCKD) results in a significantly shorter time to achieve 5% body weight loss compared to a Mediterranean diet (MD).

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to randomization concern and lack of intention-to-treat analysis)

BRIEF BACKGROUND INFORMATION: Multiple studies have found MD and VLCKD to be beneficial for desired weight loss. However, VLCKD is an infrequent recommendation by health care providers due to its lack of research on key variables, such as motivation, feasibility, and self-efficacy. Additionally, minimal studies have evaluated the effects of anthropometric factors while reaching a 5% body weight loss.

PATIENTS: Overweight or obese adults

INTERVENTION: VLCKD

CONTROL: MD

PRIMARY OUTCOME: Time to achieve 5% weight loss

Secondary Outcome: Anthropometric characteristics

METHODS (BRIEF DESCRIPTION):

- 374 adults, 18–70 years old with BMI >25 kg/m^2 in Rome, Italy, from December 2021 to May 2022 were included in the study.
- Participants received standardized nutritional counseling and then were randomized into a VLCKD or an MD diet protocol for three months or until 5% weight loss was achieved.
  - Data was collected upon entry and monthly.
- Weight measurements were taken after a 12-hour fast, with underwear only. Waist circumference was measured at the mid-point between the last rib and the iliac crest.
- To analyze body composition, bioelectrical impedance analysis was measured after a 12-hour fast on entry, then monthly until 5% weight loss or for a maximum of three months.
  - Exam parameters included total body water and fat mass.
- For VLCKD, total energy expenditure (TEE) was calculated to average 1,500 kcal for women and 1,700 kcal for men.
  - Macronutrient composition: 15% protein, 30–35% lipids, 50–55% carbohydrates, and <15% simple sugars.
  - Diet was divided into five meals per day, including vegetables, whole grain cereals, fish, legumes, lean white meat, seeds, red meat, eggs, dairy, and extra virgin olive oil 30 mL (women) and 40 mL (men) daily. Daily water intake was 2 L (women) or 2.5 L (men).
- For MD, TEE was calculated to average <800 kcal with <30–50 g of carbohydrate per day and 1.2–1.5 g of protein per kg ideal body weight per day.
  - Intake was divided between four (women) or five (men) daily meals. The diet included meal replacements for breakfast and snacks and white or red meat, fish, eggs, smoked salmon, ham, or canned fish for lunch and dinner with vegetables and extra virgin olive oil of 30 g per day. Vitamins were prescribed. A water intake of 2 L (women) and 2.5 L (men) was recommended.
- A Pearson test was utilized to evaluate the normality distribution. Paired and unpaired student t-tests were performed for intragroup and intergroup comparisons.

INTERVENTION (# IN THE GROUP): 135

COMPARISON (# IN THE GROUP): 133

FOLLOW-UP PERIOD: Three months

RESULTS:

Primary Outcome –

- A VLCKD achieved 5% weight loss in one month compared to three months for a MD (7.2% vs 7.7%, respectively; *P*<.0001).

Secondary Outcome –

- A VLCKD resulted in a smaller reduction in waist circumference compared to an MD (–5.7 cm vs –6.8 cm, respectively; *p*=.001).
- A VLCKD resulted in a smaller reduction in fat mass compared to an MD (−2.2% vs –3.2%, respectively; *p*=.0006).
- A VLCKD had a smaller increase in total body water compared to an MD (1.6% vs 2.3%, respectively; *p*=.002).
- Women on a VLCKD had a smaller reduction in waist circumference compared to an MD (–5.5 cm vs –6.8 cm, respectively; *p*=.002).
- Women on the VLCKD had a smaller decrease in fat mass compared to MD (–2.2% vs –3.3%, respectively; *p*=.003).
- All parameters between the VLCKD and the MD in men did not result in significant differences.
- Participants <50 years old on a VLCKD had a smaller reduction in waist circumference compared to an MD (5.8 cm vs 7.0 cm, respectively; *p*=.008).
- Participants <50 years old had a smaller increase in total body water compared to the MD (1.5% vs 2.4%, respectively; *p*=.004).
- No significant differences were observed in waist circumference, total body water, or fat mass with either diet in subjects >50 years old.

LIMITATIONS:

- Volunteer, recall, and self-reporting biases.
- Short study duration
- Limited demographic stratification.
- Concerns for randomization.
- No intention to treat analysis.
- Predisposed population to MD.

Owen Strom, MD, MPH
Trios Health FMRP
Kennewick, WA