GEMs of the Week

Volume 3 - Issue 35

What's in this week's issue?

Week of August 28 - September 1, 2023

SPOTLIGHT: Induction at 39 Weeks Could Be Worth It

- In the Pediatric Population, Concussion Increases Risk of Developing New Mental Health Disorders
- The Balance Between Aquatic Exercise and Land Exercise in the Geriatric Population
- Middle Aged and Still Smoking: Are There Benefits to Switching to E-Cigarettes?
- Sotatercept, a Potential Game Changer for Pulmonary Vascular Remodeling
- Methenamine Hippurate as an Alternative to Antibiotics for Recurrent UTI Prevention

Induction At 39 Weeks Could Be Worth It

Comparison of Maternal Labor-Related Complications and Neonatal Outcomes Following Elective Induction of Labor at 39 Weeks of Gestation vs Expectant Management: A Systematic Review and Meta-analysis

Hong J, Atkinson J, Roddy Mitchell A, et al. Comparison of Maternal Labor-Related Complications and Neonatal Outcomes Following Elective Induction of Labor at 39 Weeks of Gestation vs Expectant Management: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2023;6(5):e2313162. Published 2023 May 1. doi:10.1001/jamanetworkopen.2023.13162

KEY TAKEAWAY: Elective induction of labor at 39 weeks improved labor and neonatal outcomes, except for shoulder dystocia in nulliparous patients.

STUDY DESIGN: Meta-analysis and systematic review

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Elective induction of labor at 39 weeks has been a high-interest topic since the release of the ARRIVE trial. Many studies have been conducted since the release of the ARRIVE trial that focuses on perinatal outcomes. This meta-analysis attempts to review maternal labor complications by including patients with a BMI higher than 30, multiparous patients, and a trial of labor after cesarean section.

PATIENTS: Pregnant patients with singleton pregnancy

INTERVENTION: Elective induction at 39 weeks

CONTROL: Expectant management

PRIMARY OUTCOME: Perineal injury, operative vaginal delivery, postpartum hemorrhage, emergency cesarean section, macrosomia, shoulder dystocia, NICU admissions, low APGAR score

METHODS (BRIEF DESCRIPTION):

- Meta-analysis and Systemic Review of 14 articles.
- Pregnant patients with singleton pregnancy.
  - Including BMI over 30, nulliparous, multiparous, trial of labor after cesarean section.
- Perinatal outcomes were analyzed between patients receiving elective induction at 39 weeks and expectant management.

INTERVENTION (# IN THE GROUP): Total included (1,625,899), Induced at 39 weeks (86,555)

COMPARISON (# IN THE GROUP): 1,539,344

FOLLOW-UP PERIOD: Not provided

RESULTS:

Primary Outcome –

- The induction group had a decrease in third- and fourth-degree perineal tears.
  - (7 studies; OR, 0.63; 95% CI, 0.49–0.81)
- The induction group had a reduced likelihood of operative vaginal delivery.
  - (8 studies; OR, 0.87; 95% CI, 0.79–0.97)
- There was no difference between groups in postpartum hemorrhage.
  - (6 studies; OR, 0.89; 95% CI, 0.77–1.0)
- There was no difference between groups in emergency cesarean sections.
  - (14 studies; OR, 0.75; 95% CI, 0.53–1.0)
- 34% decrease in macrosomia in the induced group.
  - (4 studies; OR, 0.66; 95% CI, 0.48–0.91)
- Decrease in low five-minute Apgar score in induction group (7 and under).
  - (4 studies; OR, 0.62; 95% CI, 0.4–0.96)
- There was no decrease in emergency cesarean sections in the induction group.
  - (14 studies; OR, 0.75; 95% CI, 0.53–1.0)
- Nulliparous women had an increased likelihood of shoulder dystocia when induced.
  - (5 studies; OR, 1.22; 95% CI, 1.0–1.5)

LIMITATIONS:

- Based on a small number of studies (14), most of which were observational.
- Due to the high number of observational studies, the results could be affected by classification bias and uncontrolled confounding variables.

Joshua Pierce, DO
Indiana University FMR
Indianapolis, IN

In the Pediatric Population, Concussion Increases Risk of Developing New Mental Health Disorders

Risk of Mental Health Problems in Children and Youths Following Concussion

Ledoux AA, Webster RJ, Clarke AE, et al. Risk of Mental Health Problems in Children and Youths Following Concussion. *JAMA Netw Open*. 2022;5(3):e221235. Published 2022 Mar 1. doi:10.1001/jamanetworkopen.2022.1235

KEY TAKEAWAY: In a pediatric population aged five to 18 years, concussion was associated with an increased risk of developing new mental health problems, psychiatric hospitalization, and self-harm compared to those with other orthopedic injuries.

STUDY DESIGN: Population-based retrospective cohort study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Concussions are a common medical complaint seen in the pediatric population, and since 2008, concussions have dramatically risen. There is limited evidence regarding the association between concussions and future mental health problems. This study aimed to investigate associations between concussions and mental health problems (MHP) in young individuals over 10 years.

PATIENTS: Individuals ages five to 18 years from 2010 to 2020 in Ontario, Canada

INTERVENTION: Concussion injury

CONTROL: Orthopedic injury

PRIMARY OUTCOME: Mental health problems (psychopathologies and psychiatric disorders)
Secondary Outcome: Psychiatric hospitalizations, self-harm, and death by suicide.

METHODS (BRIEF DESCRIPTION):

- This retrospective study examined individuals between the ages of five and 18 years who presented to the ED, primary care clinic, or mental health clinician between 2010 and 2020 in Ontario, Canada.
- Healthcare and demographic data were gathered and analyzed to identify index events, and two cohorts were identified.
    - Concussion (diagnosed in the emergency department or primary care office)
    - Orthopedic injury (only injuries managed non-operatively to eliminate the possibility of sedation or exposure to opioids, which has also been associated with mental health illnesses).
    - Using a matching algorithm, cohorts were matched at a 1:2 ratio on age and sex.
- Inclusion criteria:
    - No previous mental health visits within the prior year
    - No prior concussion within the five years prior to the index event
    - For participants with more than one event, the first diagnosed concussion or injury was selected as the index event.
- Exclusion criteria:
    - Lack of continuous insurance through Ontario's universal health system within the five years prior to the index event
    - Death date before or on the index event date
    - Hospitalized with a mental health outcome on the day of the concussion or injury
- Follow-up began at the index event, and individuals were followed until they experienced a study outcome, death, loss of insurance or end of study period (range one month to 10 years).
- Mental health outcomes were obtained via databases through the Canadian Institute for Health.
    - Mental health conditions were anxiety and neurotic disorders, adjustment reactions, behavioral disorders, mood and eating disorders, schizophrenia, substance use disorder, suicidal ideation, and disorders of psychological development.
- Hazard ratios and 95% confidence intervals comparing the incidence of outcomes were computed and adjusted for socioeconomic status, child abuse/neglect, migraine, organic mental disorders, developmental disorders, and pediatric complex chronic conditions.

INTERVENTION (# IN THE GROUP): 152,321

COMPARISON (# IN THE GROUP): 296,482

FOLLOW-UP PERIOD: Up to 10 years (April 1, 2010 to March 31, 2020)

RESULTS:

Primary Outcome –

- A significant association was found between concussion and mental health problems.
- Incidence rates:
  - Exposed group (11,141; 95% CI, 11,048–11,236) per 100,000 person-years
  - Comparison group (7,960; 95% CI, 7,905–8,015) per 100,000 person-years
  - Difference (3,181; 95% CI, 3,073–3,291) per 100,000 person-years
  - Adjusted hazard ratio [aHR] (1.39; 95% CI, 1.37–1.4)

Secondary Outcome –

- Development of self-harm: A significant association was found between concussion and self-harm.
  - Incidence rate:
    - Exposed group (475; 95% CI, 459–492] per 100,000 person-years
    - Comparison group (327; 95% CI, 317–327) per 100,000 person-years
    - Difference (148; 95% CI, 128–168) per 100,000 person-years
    - Adjusted hazard ratio [aHR] (1.5; 95% CI, 1.4–1.6)
- Psychiatric hospitalization: A significant association was found between concussion and psychiatric hospitalization.
  - Incidence rate:
    - Exposed group (623; 95% CI, 604–643) per 100,000 person-years
    - Comparison group (434; 95% CI, 442–446) per 100,000 person-years
    - Difference (190; 95% CI, 167–212) per 100,000 person-years
    - aHR (1.47; 95% CI, 1.4–1.5)
- Death by suicide: No statistical significance between groups.
  - aHR ratio (1.54, 95% CI, 0.9–2.6)

LIMITATIONS:

- Health outcomes were defined using diagnosis codes in health administrative databases, which could introduce exposure or outcome misclassification.
- The study did not account for potentially compounding social factors such as familial support or anxiety, coping skills, psychosocial consequences of post-concussion symptoms, etc.
- Unable to exclude those who had medical exposure to opioids prior to the index event, which could have been the culprit for developing mental health disorders.

Katie Dalgamouni, DO
PeaceHealth Family Medicine of Southwest Washington
Vancouver, WA

The Balance Between Aquatic Exercise and Land Exercise in the Geriatric Population

A Systematic Review and Meta-analysis Comparing the Effect of Aquatic and Land Exercise on Dynamic Balance in Older Adults

Kim Y, Vakula MN, Waller B, Bressel E. A systematic review and meta-analysis comparing the effect of aquatic and land exercise on dynamic balance in older adults. *BMC Geriatr*. 2020;20(1):302. Published 2020 Aug 25 doi:10.1186/s12877-020-01702-9

KEY TAKEAWAY: Aquatic exercise (AE) is equivalent to land exercise (LE) in improving dynamic balance in adults 65 years old or older.

STUDY DESIGN: Systematic review and meta-analysis of 10 randomized controlled trials (RCTs)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small effect size and inconsistency between data)

BRIEF BACKGROUND INFORMATION: Approximately 30% of individuals older than 65 years old fall every year, which can primarily be attributed to balance impairments. Aquatic exercise (AE) is an available alternative to land exercise (LE). AE can be particularly helpful for patients with lower physical activity levels, neuromuscular disorders, or orthopedic disabilities that affect balance, mobility, and pain. AE has been shown to improve strength, mobility, flexibility, and other health benefits.

PATIENTS: Adults 65 years old and older

INTERVENTION: AEs

CONTROL: LEs

PRIMARY OUTCOME: Dynamic balance improvements

METHODS (BRIEF DESCRIPTION):

- The mean age of patients was 69.6 years old. No other demographic information was provided.
- Inclusion criteria: RCTs, published in the English language, including at least one AE and one LE group, and at least one outcome related to dynamic balance.
- Intervention: AE and LE programs varied substantially across trials but ranged from 1–5 times a week, lasting 45-60 min each session over 4–20 weeks in total duration.
- Dynamic balance improvements were calculated using the 5-m walk test, 10-m walk test, and backward tandem walk. Balance improvements were assigned in the following three categories.
  - Dynamic steady-state balance (ability to maintain balance during movement)
  - Proactive balance (preparation for and anticipation of disruptions in balance)
  - Balance test batteries (a series of tests to assess a person's balance and gait)
- Pooled effect sizes between AE and LE groups were described as standardized mean differences (SMD).
- Effect sizes (SMDs) were categorized into three groups:
  - Small effect (0.2–0.5)
  - Moderate effect (0.5–0.8)
  - Large effect (>0.8)

INTERVENTION (# IN THE GROUP): 192

COMPARISON (# IN THE GROUP): 180

FOLLOW-UP PERIOD: 17 days to 12 months

RESULTS:

Primary Outcome –

- There were no significant differences in balance improvements between AE and LE groups.
  - Dynamic steady-state balance (3 trials, n=93; SMD –0.24, 95% CI, –0.81 to 0.34; I^2=40%)
  - Proactive balance (9 trials, n=266; SMD –0.21, 95% CI, –0.59 to 0.17; I^2=56%)
  - Balance test balance (7 trials, n=221; SMD –0.24, 95% CI, –0.50 to 0.03; I^2=0%)

LIMITATIONS:

- Trials had a risk of bias due to the randomization process, missing outcomes data, and selection of the reported results. This may have led to an overestimation of the true effects of AE and LE.

Jafar Ohiokpehai, MD
Saint Louis University Southwest Illinois FMR
O'Fallon, IL

Middle Aged and Still Smoking: Are There Benefits to Switching to E-Cigarettes?

Is E-Cigarette Use Associated with Better Health and Functioning Among Smokers Approaching Midlife?
Kosterman R, Epstein M, Bailey JA, Hawkins JD. Is e-cigarette use associated with better health and functioning among smokers approaching midlife? *Drug Alcohol Depend*. 2022;234:109395. doi:10.1016/j.drugalcdep.2022.109395

KEY TAKEAWAY: Smokers 30–39 years old who switched to vaping or offset combustible smoking with vaping were found to have better health and well-being than those who purely used combustible cigarettes.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Among smokers, few studies have shown the impact of e-cigarette use on the health and functioning of individuals 30–39 years old. This study sought to better understand the impact on smokers in midlife.

PATIENTS: Adults who smoke combustible cigarettes

INTERVENTION: Patients who replaced or supplemented combustible cigarettes with e-cigarettes

CONTROL: Patients who smoked combustible cigarettes 30–39 years old

PRIMARY OUTCOME: Health and function of middle-aged smokers

METHODS (BRIEF DESCRIPTION):

- Adults 30–39 years old using nicotine were recruited from the Seattle social development project.
- This sample was 54% male, 49% European American, 26% African American, 15% Asian American, and 11% Native American, and across race, 6% were of Hispanic ethnicity.
- Nicotine users were divided into two groups. One group consisted of individuals who used combustion cigarettes (and no other type of nicotine) with individuals 30–39 years old. The other group consisted of individuals who switched from, or supplemented combustion cigarette use with e-cigarette use during this same age period of individuals 30–39 years old. 95% of e-cigarette usage reported was 30 times or fewer in the past month.
- The health and functioning of each participant were assessed at 39 years old and compared with a corresponding set of results from 30 years old. This assessment was done using nine separate scales associated with nine specific health and functioning outcomes. These outcomes were:
  - Personal experience, fewer alcohol problems, fewer drug problems, constructive engagement, civic engagement, the number of nonsmoking partners and peers, mental health, physical health, and socioeconomic status.
- The results of each scale were then simplified to facilitate comparison by using a 0–1 code, with one indicating the healthiest or most positive result in that outcome category.

INTERVENTION (# IN THE GROUP): 56

COMPARISON (# IN THE GROUP): 100

FOLLOW-UP PERIOD: 9 years

RESULTS:

Primary Outcome –

- The results of this study indicate that higher vaping frequency relative to smoking combustion cigarettes was associated significantly with improvements in the following outcomes:
  - Increased exercise: beta 0.18, *P*=.036
  - Constructive engagement: beta 0.13, *P*=.009
  - Physical health: beta 0.18, *P*=.013
  - Socioeconomic status: beta 0.16, *P*=.007
- There was found to be a moderate increase in civic engagement for 39 years old associated with higher vaping frequency relative to combustion cigarette use.
  - Civic engagement: beta 0.15, *P*=.067
- There were no significant associations found regarding alcohol problems, drug problems, non-smoking partners and peers, or mental health.

LIMITATIONS:

- The sample in this study was taken from a single community project in Seattle. This could decrease generalizability.
- This study does not tell us about the intervening years, so we do not know the timeframes of the vaping initiation.

- The collected data predates the introduction of popular/large e-cigarette companies such as JUUL, and may not reflect the most recent form of e-cigarettes.
- Individuals who quit nicotine entirely were not examined and compared in this study.
- The nature of this analysis does not address cause and effect when considering the relationship between vaping and health measures.

Christopher Ingram, DO
Cahaba UAB Family Medicine Residency
Centreville, AL

Sotatercept, a Potential Game Changer for Pulmonary Vascular Remodeling

Sotatercept for the Treatment of Pulmonary Arterial Hypertension

Humbert M, McLaughlin V, Gibbs JSR, et al. Sotatercept for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2021;384(13):1204-1215. doi:10.1056/NEJMoa2024277

KEY TAKEAWAY: In patients with pulmonary arterial hypertension, 24 weeks of treatment with sotatercept improves pulmonary vascular resistance compared to placebo.

STUDY DESIGN: Phase 2 randomized, double-blind, placebo-controlled

LEVEL OF EVIDENCE: STEP 3 (downgraded due to decreased power of the study)

BRIEF BACKGROUND INFORMATION: Pulmonary arterial hypertension is a debilitating disorder. However, the current therapies only provide a 60% five-year survival rate. Several clinical trials have investigated the safety and efficacy of sotatercept, a potential treatment for pulmonary arterial hypertension.

PATIENTS: Patients with pulmonary arterial hypertension

INTERVENTION: Subcutaneous sotatercept

CONTROL: Placebo (subcutaneous saline)

PRIMARY OUTCOME: Improvement in pulmonary vascular resistance

Secondary Outcome: The change in six-minute walk distance at 24 weeks compared to baseline

METHODS (BRIEF DESCRIPTION):

- Patients were stratified according to WHO functional class and randomly assigned in a 1:1:1 ratio: sotatercept at 0.3 mg/kg, 0.7 mg/kg, or placebo.
  - The assignment was changed to a 3:3:4 ratio to increase the statistical power of the sotatercept 0.7-mg/kg group.
- Patients were excluded if their pulmonary HTN subtype was associated with portopulmonary disease, schistosomiasis, or HIV infection.
- Each participant received standard of care plus subcutaneous sotatercept or placebo for 24 weeks.
- Dosing was every three weeks and based on body weight, and after 24 weeks, there was an 18-month extension and an eight-week follow-up period.
  - Subjects received sotatercept at a dose of 0.3 mg/kg of body weight or 0.7 mg/kg.
- The primary outcome was the difference in the measured pulmonary vascular resistance at baseline and 24 weeks.
- The secondary outcome was the difference in the distance walked during the six-minute walk test at baseline, and the distance walked at 24 weeks.

INTERVENTION (# IN THE GROUP): Sotatercept 0.3 mg/kg (32)**,** Sotatercept 0.7 mg/kg (42)

COMPARISON (# IN THE GROUP): Placebo and standard care (32)

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- Patients who received the regimen of 0.3 mg/kg of sotatercept significantly improved pulmonary vascular resistance compared to those who received a placebo (mean difference of –146 dyn·sec·cm−5; 95% CI, –241 to –51).
- Patients who received the regimen of 0.7 mg/kg of sotatercept significantly improved pulmonary vascular resistance compared to those who received a placebo (mean difference of –240 dyn·sec·cm−5; 95% CI, −329 to −150).

Secondary Outcome –

- The mean difference between sotatercept 0.3 mg/kg group and the placebo group at 24 weeks was 29.4 m (95% CI, 3.8–55).
- The least-squares mean difference between the sotatercept 0.7 mg/kg group and the placebo group was 21.4 m (95% CI, −2.8 to 46).

LIMITATIONS:

- The sample size was small, decreasing the power of the study.
- The duration of the study was brief, reducing generalizability and increasing confounding factors.
- Patients have different etiologies of pulmonary arterial hypertension, which can affect their response to treatment and limit the efficacy of the medication.

Navdeep Sharma, MD
Good Samaritan Regional Medical Center FMR
Corvallis, OR

Methenamine Hippurate as an Alternative to Antibiotics for Recurrent UTI Prevention

Alternative to Prophylactic Antibiotics for the Treatment of Recurrent Urinary Tract Infections in Women: Multicentre, Open Label, Randomised, Non-Inferiority Trial

Harding C, Mossop H, Homer T, et al. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open-label, randomised, non-inferiority trial. *BMJ*. 2022;376:e068229. Published 2022 Mar 9. doi:10.1136/bmj-2021-0068229

KEY TAKEAWAY: Preventive treatment with methenamine hippurate for women with recurrent UTIs is non-inferior to standard of care daily, low-dose antibiotics.

STUDY DESIGN: Randomized, open-label, non-inferiority trial, multicenter

LEVEL OF EVIDENCE: STEP 3 (downgraded for lack of blinding, small sample size)

BRIEF BACKGROUND INFORMATION: Daily antibiotic prophylaxis is the current standard of care for recurrent UTIs in women. However, long-term antibiotic use can lead to potential antibiotic resistance, prompting further studies on alternative therapies. One is the non-antibiotic alternative methenamine hippurate, a drug converted to bactericidal formaldehyde in acidic environments such as urine.

PATIENTS: Women with recurrent UTI requiring prophylactic treatment

INTERVENTION: Methenamine hippurate

CONTROL: Antibiotic prophylaxis

PRIMARY OUTCOME: Incidence of symptomatic antibiotic-treated UTI

Secondary Outcome: Incidence of symptomatic antibiotic-treated UTI in the six months after treatment, microbiologically confirmed UTI, antibiotic resistance profiles to E. coli, asymptomatic bacteriuria, total antibiotic use, and hospital admissions due to UTI

METHODS (BRIEF DESCRIPTION):

- Participants were women ages 18 years and over (mean 50 years old) with recurrent UTIs from urology and urogynecology clinics in the United Kingdom.
- Participants with correctable abnormalities (such as urinary tract calculi) or neurogenic dysfunction of the urinary tract were excluded.
- Participants were randomized into antibiotic prophylaxis (control group) with nitrofurantoin 50 or 100 mg daily, trimethoprim 100 mg daily, or cephalexin 250 mg daily vs. methenamine hippurate (intervention group) 1 g twice daily.
- Follow-up visits occurred every three months until month 18. Outcomes were measured based on the incidence of re-occurrence of symptoms, incidence of antibiotic-treated UTI, adherence to assigned treatment ≥90%, incidence of adverse events, incidence of abnormal lab tests in the urine sample, and kidney and liver function.

INTERVENTION (# IN THE GROUP): 103

COMPARISON (# IN THE GROUP): 102

FOLLOW-UP PERIOD: 18 months

RESULTS:

Primary Outcome –

- There was no statistically significant difference in the incidence of self-reported symptomatic, antibiotic-treatment UTI episodes between the methenamine hippurate group vs. the antibiotic prophylaxis group (1.38 episodes per person-year vs. 0.89, respectively).
  - (Absolute difference of 0.49; 90% CI, 0.15–0.84)
  - This indicates that methenamine hippurate is non-inferior to antibiotic prophylaxis.
- There was no statistically significant difference between the groups in incidence of symptomatic antibiotic-treated UTI six months after treatment, microbiologically confirmed UTI, antibiotic resistance profiles to E. coli, asymptomatic bacteriuria, total antibiotic use, and hospital admissions due to UTI.
  - Satisfaction with treatment was similar in both groups.

LIMITATIONS:

- There was no blinding, and participants could switch between the treatment and control groups.
- Multiple types of prophylactic antibiotics were used, and there was no specific analysis of the efficacy of one particular antibiotic.

- There is a lack of robust long-term safety data on using methenamine hippurate.
- There was a limited number of study participants from only one country, which may impact generalizability.

Asta Jakobsson, DO
Abrazo Health Network
Phoenix, AZ