GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 1 - Issue 41

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of October 11 - 15, 2021

SPOTLIGHT: Progestogens for Preventing Preterm Birth - Does it Really Work?

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Progestogens for Preventing Preterm Birth: Does It Really Work?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Evaluating Progestogens for Preventing Preterm Birth International Collaborative (EPPPIC): Meta-Analysis of Individual Participant Data from Randomised Controlled Trials

EPPPIC Group. Evaluating Progestogens for Preventing Preterm Birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials [published correction appears in *Lancet*. 2021 Apr 17; 397(10283):1446]. *Lancet*. 2021; v397(10280):1183–1194. doi:10.1016/S0140-6736(21)00217-8

KEY TAKEAWAY: Vaginal progestogens reduced the risk of preterm birth, low birth weight, NICU admission, and neonatal respiratory support. Intramuscular 17-OHPC had no effect on these same outcomes but increased the risk of preterm premature rupture of membranes in multi-fetal gestations.

STUDY DESIGN: Meta-analysis of 31 randomized controlled trials

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Preterm birth is a major cause of morbidity and mortality in the newborn period and beyond. Progesterone decline has been theorized to play a role in triggering labor so supplemental progestogens provide an opportunity to sustain a pregnancy though this critical period.

PATIENTS: Asymptomatic pregnant individuals at high risk of preterm birth

INTERVENTION: Supplemental progestogens

CONTROL: Placebo or standard care

OUTCOME: Preterm birth, adverse neonatal outcomes, adverse maternal outcomes

METHODS (BRIEF DESCRIPTION):

- Vaginal progesterone, intramuscular 17-hydroxyprogesterone caproate (17-OHPC), and oral progesterone were compared with control and each other.
- 11,644 pregnant individuals and 16,185 offspring were identified.
- Separate analyses were performed for vaginal progesterone (14 trials), 17-OHPC (13 trials), and oral progesterone (2 trials), as well as singleton and multifetal pregnancies.
    - Singleton pregnancy trials included mostly individuals with prior spontaneous preterm birth or short cervix.
- The primary outcome of preterm birth was separated into groups: preterm birth at <37 weeks, early preterm birth at <34 weeks, and mid-trimester birth at <28 weeks.
- Adverse Neonatal Outcomes: Respiratory distress syndrome, neonatal respiratory support, birthweight, and NICU admission.
- Adverse Maternal Outcomes: Gestational hypertension, pre-eclampsia, gestational diabetes, and maternal infection.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Patients were followed into the early newborn period to assess for neonatal complications.

RESULTS:

- Vaginal progesterone supplementation reduced early preterm birth in high-risk pregnancies (9 trials, N=3,769; RR 0.78; 95% CI, 0.68–0.90).
- Oral progesterone reduced early preterm birth (2 trials, N=181; RR 0.60; 95% CI, 0.40–0.90).
- Vaginal progesterone reduced the risk of:
    - Low birthweight <2,500 g (RR 0.82; 95% CI, 0.74–0.91)
    - Very low birthweight <1,500 g (RR 0.70; 95% CI, 0.49–0.99)
    - NICU admission (RR 0.78; 95% CI, 0.68–0.90)
    - Respiratory support (RR 0.77; 95% CI, 0.61–0.99)
- Vaginal progesterone did not reduce the risk of neonatal mortality, maternal complications, or preterm birth for multifetal gestations.
- 17-OHPC did not significantly impact the following outcomes: Birthweight, NICU admission, respiratory support, early preterm birth, neonatal mortality, maternal complications, or preterm birth for multifetal gestations.
- However, 17-OHPC exposure was associated with preterm premature rupture of membranes in multifetal gestations (RR 1.6; 95% CI, 1.2–2.2).

LIMITATIONS: This study did not suggest a specific protocol for supplementing progestogens, limiting use in clinical situations, and providing opportunities for further study.

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Does Sotagliflozin Improve Cardiovascular Outcomes in Patients with Diabetes and Worsening Heart Failure?

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. 2021; 384(2):117–128. doi:10.1056/NEJMoa2030183

KEY TAKEAWAY: Sotagliflozin initiated before or shortly after discharge in patients with diabetes and recent worsening heart failure results in significantly fewer urgent care visits for heart failure, hospitalizations for heart failure, and deaths from cardiovascular causes compared to placebo.

STUDY DESIGN: Multicenter, double blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: SLGT2 inhibitors reduce the risk of hospitalization for heart failure exacerbations in patients with type II diabetes. In patients with heart failure, SGLT2 inhibitors also reduce the risk of death from cardiovascular causes or hospitalization for heart failure, regardless of whether they have diabetes. However, the safety and efficacy of initiating an SGLT2 inhibitor soon after an episode of decompensated heart failure remains uncertain.

PATIENTS: Adults 18–85 years old with type II diabetes and recent hospitalization for heart failure

INTERVENTION: 200 mg Sotagliflozin

CONTROL: Placebo

OUTCOME: Composite of deaths from cardiovascular causes, hospitalizations for heart failure, urgent care visits for heart failure

Secondary Outcomes: Cardiovascular causes, quality of life

METHODS (BRIEF DESCRIPTION):

- Patient Demographics:
  - Median age 69
  - Predominantly male, White, and European
  - Median HbA1c 7.1% and LVEF 35%.
- Exclusion criteria: End-stage heart failure, recent acute coronary syndrome, stroke, PCI, CABG, GFR <30 mL/min
- 1,222 patients randomly assigned to placebo or Sotagliflozin.
  - Sotagliflozin: 200 mg P.O. once daily within 3 days of discharge, with dose increase to 400 mg, depending on side effects.
- Quality of life measured with Kansas City Cardiomyopathy Questionnaire (KCCQ) ranging from 0 to 100, with higher scores indicating better quality of life.

INTERVENTION (# IN THE GROUP): 608

COMPARISON (# IN THE GROUP): 614

FOLLOW UP PERIOD: Median 9.2 months

RESULTS:

- The Sotagliflozin group had significantly fewer deaths from cardiovascular causes compared to the placebo group (HR 0.67; 95% CI, 0.52 to 0.85; NNT=4).
- Sotagliflozin compared to placebo resulted in fewer hospitalizations and urgent care visits for heart failure (HR 0.64; 95% CI, 0.49–0.83; NNT=4).
- Sotagliflozin led to a greater improvement in quality of life compared to placebo (MD 4.1; 95% CI, 1.3–7.0).
- However, Sotagliflozin did not significantly affect the rates of death from cardiovascular causes or death from any cause.

LIMITATIONS:

- Early termination due to loss of trial funding led to insufficient power to test for death from cardiovascular causes or hospitalization for heart failure.
- A mean difference of 4.1 on a 100-point scale for KCCQ may not be clinically meaningful.

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Self-Reported Penicillin Allergy in Pregnancy: Should We Test in Clinic?

Outpatient Penicillin Allergy Testing in Pregnant Women Who Report an Allergy

Desravines N, Waldron J, Venkatesh KK, Kwan M, Boggess KA. Outpatient penicillin allergy testing in pregnant women who report an allergy. *Obstet Gynecol*. 2021; 137(1):56–61.

KEY TAKEAWAY: Outpatient penicillin allergy testing is feasible, acceptable, and safe in pregnant women.

STUDY DESIGN: Prospective cohort study at a single healthcare system

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: During pregnancy, antibiotics are given to 30–74% of women for various indications. More commonly used antibiotics in pregnancy include penicillin and other beta lactams, clindamycin, other macrolides, and aminoglycosides. Increased risk for antibiotic resistance and maternal morbidity is seen in pregnant women with self-reported penicillin allergy and typically receive broader spectrum antibiotic alternatives like cefazolin, clindamycin, and vancomycin.

PATIENTS: Pregnant women with self-reported penicillin allergy

INTERVENTION: Three-step penicillin allergy testing

CONTROL: No testing

OUTCOME: Feasibility, acceptability, and safety

METHODS (BRIEF DESCRIPTION):

- Self-reported penicillin allergy in English or Spanish speaking pregnant women 18 to 55 years old at 14 0/7 to 36 6/7 weeks' gestation with no known fetal abnormalities (n=127).
- Exclusion criteria: Prior positive penicillin allergy test results or anaphylaxis within previous year.
- A three-hour three-step protocol was performed by an allergist to test for penicillin allergy.
    - Step 1: Skin prick with controls (saline and histamine) and penicillin G and Pre-pen (benzylpenicilloyl polylysine).
        - Positive skin test = >3 mm wheal greater than saline control. Confirmed penicillin allergy noted.
        - Negative skin test = Proceed to step 2.
    - Step 2: Intradermal injection with controls (saline and histamine) and penicillin G and Pre-pen (benzylpenicilloyl polylysine).
        - Positive skin test = >5 mm than initial wheal. Confirmed penicillin allergy noted.
        - Negative skin test = Proceed to step 3.
    - Step 3 (gold standard): Graded oral amoxicillin challenge
        - Allows for confirmation of penicillin tolerance.
- If >10% of tested women experienced serious adverse reactions or anaphylaxis, the study would have been terminated.

INTERVENTION (# IN THE GROUP): 50

COMPARISON (# IN THE GROUP): 77

FOLLOW UP PERIOD: Through delivery

RESULTS:

Primary Outcome –

- Outpatient penicillin allergy testing is feasible and acceptable in pregnant women, with 58% of women agreeing to testing and 68% of those women followed through with testing (95% CI, 56–78%; alpha error 5%).

Secondary Outcome –

- 93% of women had negative test results for penicillin allergy (95% CI, 68–100%).
- 4% of women tested were confirmed to have a severe allergy to penicillin (95% CI, 0.5–15%).
- Zero deaths were observed (95% CI, 0–8%).

LIMITATIONS:

- Time commitment and distance from the clinic due to rural settings.
- Small sample size limits safety analysis for rare outcomes, such as death, systemic reaction, and anaphylactic allergic reaction.
- Larger studies are needed to improve comprehension of current rates of anaphylaxis.

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Exercise and Lower Back Pain: Is It Working Out?

Exercise is Medicine, but Perhaps Not for Preventing Low Back Pain: A Randomized Trial of Exercise and Education to Prevent Low Back Pain Recurrence

Ferreira GE, Lin CC, Stevens ML, et al. Exercise is Medicine, but Perhaps Not for Preventing Low Back Pain: A Randomized Trial of Exercise and Education to Prevent Low Back Pain Recurrence. *J Orthop Sports Phys Ther*. 2021; 51(4):188–195. doi:10.2519/jospt.2021.10187

KEY TAKEAWAY: In-person exercise and education did not provide a greater reduction in lower back pain (LBP) pain recurrence compared to an educational booklet.
STUDY DESIGN: Randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Recurrent episodes of LBP causes a significant loss in time at work, accounting for 69% of all work lost in the U.S. These episodes are also expensive, with 84% of U.S.'s medical costs attributing to LBP. Previous studies on LBP treatment have been of low quality.

PATIENTS: Adults who had recovered from LBP within the past week
INTERVENTION: Exercise and education program
CONTROL: Educational booklet
OUTCOME: Time to recurrence of LBP
Secondary Outcome: Time to recurrence of LBP leading to activity limitation, care seeking, and work absence

METHODS (BRIEF DESCRIPTION):

- Participants were randomly assigned in a 1:1 ratio to an exercise and education program or an educational booklet.
  - Exercise and Education Program: For 12 weeks a physical therapist led group-based exercise sessions, home exercise sessions, and one-on-one sessions focusing on cardiovascular, flexibility, resistance, and neuro-motor exercises.
  - Educational Booklet: Information on self-management and prevention strategies (including exercise) alone with one appointment with physical therapist.
- Researchers collecting and analyzing data were blinded to treatment groups of the participants
- Primary Outcome: An episode of pain lasting for at least 24 hours with a pain intensity of 30 or more on a 0–100 pain-rating scale

INTERVENTION (# IN THE GROUP): 57
COMPARISON (# IN THE GROUP): 54

FOLLOW UP PERIOD: 1 year

RESULTS:

- The exercise and education group compared to the educational booklet group did not differ in the following areas:
  - Time to recurrence (HR 1.1; 95% CI, 0.7–1.8)
  - Activity limitation (HR 0.96; 95% CI, 0.5–1.7)
  - Care seeking (HR 0.68; 95% CI, 0.3–1.3)
  - Work absence (HR 0.93; 95% CI, 0.4–2.2)
  - Adverse events (5 vs 1 respectively; *P*=.2)

LIMITATIONS:

- Planned to include 160 but only were able to include 111, affecting precision of the treatment effect estimates.
- Adherence to exercise program was low (55%).

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Does Early Referral for Suspected Cancer Really Make a Difference?

Association Between Use of Urgent Suspected Referral and Mortality and Stage at Diagnosis

Round T, Gildea C, Ashworth M, Møller H. Association between use of urgent suspected cancer referral and mortality and stage at diagnosis: a 5-year national cohort study. *Br J Gen Pract*. 2020; 70(695): e389–e398. Published 2020 May 28. doi:10.3399/bjgp20X709433

KEY TAKEAWAY: Early urgent referral of suspected cancer is possibly associated with lower mortality and lower risk of late-stage cancer when diagnosed.

STUDY DESIGN: Retrospective five-year cohort study

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: The promptness of primary care providers to refer to specialty care for suspected cancer may impact the stage and prognosis of cancer upon diagnosis. Little research has been done to quantify the potential benefit of early urgent suspected cancer referrals on mortality risk.

PATIENTS: Adult cancer patients

INTERVENTION: Primary care practices with high utilization of urgent referral pathways for suspected cancer

CONTROL: Primary care practices with low utilization of urgent referral pathways for suspected cancer

OUTCOME: Primary – Cancer stage at diagnosis, III/IV vs I/II

Secondary – Five-year mortality

METHODS (BRIEF DESCRIPTION):

- >1.4 million patients diagnosed with cancer in England between 2011 and 2015 of all severity and stages.
- Practices were divided into quintiles based on referral ratios (how often a practice referred a suspected cancer diagnosis), detection rates (proportion of cancers diagnosed from urgent referrals), and conversion rates (the proportion of urgent referrals resulting in a cancer diagnosis).
- Late-stage cancer risk and mortality risk for each quintile were reported for all cancers and the four most common cancer types (colorectal, lung, breast, prostate).

INTERVENTION (# IN THE GROUP): 283,398 (highest urgent referral quintiles)

COMPARISON (# IN THE GROUP): 283,567 (lowest urgent referral quintiles)

FOLLOW UP PERIOD: Five years

RESULTS:

- 5-year cancer mortality risk was significantly lower in practices with the highest referral ratios compared to practices with lowest referral ratios (HR 0.96; 95% CI, 0.96–0.97), even when adjusted for cancer stage (HR 0.98; 95% CI, 0.97–0.98).
- The odds of diagnosing late-stage vs early-stage cancer were significantly lower in practices with the highest referral ratios compared to practices with the lowest referral ratios (OR 0.97; 95% CI, 0.95–0.98), except in the subgroup analysis for colorectal cancer.

LIMITATIONS:

- Variations in case-mix and yearly differences in urgent referrals for suspected cancer could affect the reliability of reported detection and conversion rates.
- A large proportion of the cohort (1/3) with missing cancer stage information questions the validity of mortality analysis.
- The study was conducted in the UK, which may not translate to US demographics due to the drastic difference in healthcare systems.

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