GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Is Progesterone Useful in Preventing Miscarriage in Early Pregnancy Bleeding?

Progesterone to Prevent Miscarriage in Women with Early Pregnancy Bleeding

Coomarasamy A, Harb HM, Devall AJ, et al. Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT. *Health Technol Assess*. 2020; 24(33):1–70. doi:10.3310/hta24330

KEY TAKEAWAY: Progesterone does not prevent early pregnancy bleeding in women with no prior history of miscarriage; however, a gradient effect is observed in women with an increasing number of miscarriages having increased rates of live birth ≥34 weeks with use of supplemental progesterone.

STUDY DESIGN: Multi-site, double-blind, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Miscarriage is the most common complication of early pregnancy with 1 of 5 clinically recognized pregnancies resulting in miscarriage. Several studies have evaluated the use of progesterone in prevention of early miscarriage and most indicated potential benefit. However, all the prior studies had low power and methodological flaws and a definitive trial with adequate power was needed.

PATIENTS: Women with early pregnancy bleeding (<12 weeks' gestation [GA])

INTERVENTION: Progesterone 400 mg BID vaginal pessary

CONTROL: Placebo pessary

PRIMARY OUTCOME: Live birth rate at ≥34 weeks gestational age

Secondary Outcomes: Ongoing pregnancy at 12 weeks, emergency cesarean delivery

METHODS (BRIEF DESCRIPTION):

- Participants were recruited from 48 United Kingdom NHS sites over the course of 27 months (2015–2018).
- Inclusion criteria: Women 16–39 years old <12 weeks' GA with early pregnancy bleeding (within 4 days of bleeding onset) with an intrauterine gestational sac visible on ultrasound.
- Exclusion criteria: CRL ≥7 mm with no visible heartbeat or mean gestational sac ≥25 mm with no visible fetal pole on ultrasound, evidence of ectopic pregnancy, life-threatening bleeding, current or recent use progesterone, or contraindications to progesterone.
- Patient demographics: Average age 31 years old, 27 kg/m^2, 89% non-smokers, 83% White
- Participants were randomized into double-blind treatment and control arms according to an electronic integrated trial management system.
  - Treatment consisted of 400 mg vaginal pessary BID initiated upon acceptance to the trial until 16 weeks' GA.
  - The control arm received a non-hormonal vaginal pessary.

INTERVENTION (# IN THE GROUP): 2,025

COMPARISON (# IN THE GROUP): 2,013

FOLLOW UP PERIOD: 28 days postpartum

RESULTS:

Primary Outcome -

- Progesterone did not affect live births ≥34 weeks compared to placebo (75% vs 72%, respectively; relative risk [RR] 1.0; 95% CI, 1.0–1.1).
- Subgroup analyses on number of prior miscarriages:
  - In women with no prior history of miscarriage, progesterone provided no benefit for live births ≥34 weeks vs placebo (75% vs 74%, respectively; RR 0.99; 95% CI, 0.95–1.0).
  - In women with history of ≥3 miscarriages there was an increase in live birth rates ≥34 weeks with use of progesterone vs placebo (72% vs 57%, respectively; RR 1.3; 95% CI, 1.1–1.5).
  - When those with no prior miscarriage were compared with ≥1 prior miscarriage, progesterone was effective at increasing live births ≥34 weeks in those with at least one prior miscarriage vs placebo (75% vs 70%, respectively; RR 1.1; 95% CI, 1.03–1.2).

Secondary Outcomes -

- Progesterone compared to placebo resulted in:
  - More ongoing pregnancies at 12 weeks (83% vs 80%, respectively; *P*=.01)
  - Fewer emergency cesarean deliveries (15% vs 19%, respectively; *P*=.006)

LIMITATIONS:

- The study only utilized progesterone 400 mg vaginal pessaries twice daily and the generalizability to other formulations or doses of progesterone is limited.
- The use of supplemental progesterone was not investigated past 16 weeks of pregnancy or in women without a confirmed intrauterine sac.

- Compliance was similar between groups but there were significant numbers of patients with missing compliance information.
- High declination rate (68%) introduced potential selection bias.

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Tirzepatide: A First-in-Class Medication for the Treatment of Obesity in Adults without Diabetes

Tirzepatide Once Weekly for the Treatment of Obesity

Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;10.1056/NEJMoa2206038. doi:10.1056/NEJMoa2206038

KEY TAKEAWAY: Tirzepatide in conjunction with appropriate lifestyle modifications results in clinically significant weight loss.

STUDY DESIGN: Phase three, multi-site, parallel, double-blinded, randomized placebo-controlled clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Obesity is one of the leading causes of morbidity and mortality in the United States and continues to be an escalating problem worldwide. Conventional non-surgical treatments in conjunction with lifestyle interventions typically result in minimal sustained weight loss, but more recent treatments have shown promise in the treatment of this complex disease process. Tirzepatide is a first-in-class dual action glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist that was evaluated as a once weekly subcutaneous injection for the treatment in adults without diabetes.

PATIENTS: Obesity or overweight with at least one weight-related complication excluding diabetes mellitus

INTERVENTION: Tirzepatide and lifestyle interventions

CONTROL: Placebo and lifestyle interventions

PRIMARY OUTCOME: Weight loss; 5% change in body weight

Secondary Outcomes: 20% weight loss; waist circumference; glycemic state

METHODS (BRIEF DESCRIPTION):

- 2,539 adults who were 18 years or older with a BMI ≥30 or BMI ≥27 with at least one weight related medical condition excluding diabetes mellitus.
- Randomized into a 1:1:1:1 ratio to receive Tirzepatide as a once weekly subcutaneous (SC) injection (5 mg, 10 mg, 15 mg) or placebo. All groups received the same lifestyle interventions. Patients were then monitored for 72 weeks in addition to a four week follow up period.
- Tirzepatide was initiated at 2.5 mg SC weekly and increased every four weeks to reach target dose.
- Lifestyle interventions included dietary counseling, a 500 calorie per day deficit, and at least 150 minutes of physical activity per week.

INTERVENTION (# IN THE GROUP): 630

COMPARISON (# IN THE GROUP): 643

FOLLOW UP PERIOD: 72 weeks intervention period with an additional four week follow up

RESULTS:

Primary Outcome:

- There was significant mean percentage change in weight loss at 72 weeks in all doses, including placebo.
  - Tirzepatide 5 mg: –15% (95% CI, –16 to –14)
  - Tirzepatide 10 mg: –20% (95% CI, –20 to –19)
  - Tirzepatide 15 mg: –21% (95% CI, –22 to –20)
  - Placebo: –3.1% (95% CI, –4.3 to –1.9)
- Patients with at least 5% weight loss at 72 weeks:
  - Tirzepatide 5 mg: 85% (95% CI, 82–89)
  - Tirzepatide 10 mg: 89% (95% CI, 86–82)
  - Tirzepatide 15 mg: 91% (95% CI, 88–94)
  - Placebo: 35% (95% CI, 30–39)

Secondary Outcomes:

- Patients with at least 20% weight loss at 72 weeks:
  - Tirzepatide 5 mg: 30% (95% CI, 26–34)
  - Tirzepatide 10 mg: 50% (95% CI, 46–54)
  - Tirzepatide 15 mg: 57% (95% CI, 53–61)
  - Placebo: 3.1% (95% CI, 1.1–5.1)
- Patients change in waist circumference at 72 weeks:
  - Tirzepatide 5 mg: –14 cm (95% CI, –15 to –13)
  - Tirzepatide 10 mg: –18 cm (95% CI, –19 to –17))
  - Tirzepatide 15 mg: –19 cm (95% CI, –19 to –18)
  - Placebo: –4.0 cm (95% CI, –5.1 to –2.8)
- In prediabetic patients, 95% of patients in the treatment groups returned to a normal glycemic state compared to 63% in the placebo group.

LIMITATIONS:

- Limited follow up period and long-term data on weight loss sustainability.
- Patient population focused on weight loss and the potential for the Hawthorne Effect. Unclear if the same dramatic results will be seen in populations without such close observation.
- United States patient population: 70% female, 81% identified as White. Demographics were self-reported.
- Excluded patient populations included those with uncontrolled medical conditions that would benefit from weight loss.

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What is the Benefit of Early CT Coronary Angiography in Intermediate-Risk Patients Presenting to the ED with Chest Pain?

Early Computed Tomography Coronary Angiography in Patients with Suspected Acute Coronary Syndrome: Randomized Controlled Trial

Gray AJ, Roobottom C, Smith JE, et al. Early computed tomography coronary angiography in patients with suspected acute coronary syndrome: randomised controlled trial [published correction appears in BMJ. 2022 Feb 21;376:o438]. *BMJ.* 2021; 374:n2106. Published 2021 Sep 29. doi:10.1136/bmj.n2106

KEY TAKEAWAY: Early CT coronary angiography in intermediate risk patients presenting to ED with acute chest pain does not improve all-cause mortality or subsequent type 1 or 4b myocardial infarction at one year.

STUDY DESIGN: Prospective, randomized, open, blinded endpoint, parallel-group clinical effectiveness trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Chest pain is a common complaint in patients presenting to the ER. Early CT coronary angiography (CTCA) is currently not part of the standard care in low to intermediate risk patients presenting to the ER with acute chest pain and provisional diagnosis of acute coronary syndrome. There have been several trials in the past that have explored the use of CTCA, some of these studies found increased rates of discharge from hospitals and shortened length of stays compared with usual care. This study aims to assess the benefit of early CTCA in this patient population.

PATIENTS: Low-to-intermediate risk patients presenting to ED with acute chest pain

INTERVENTION: Early CTCA plus standard of care

CONTROL: Standard of care

PRIMARY OUTCOME: All-cause mortality or subsequent type 1 or 4b myocardial infarction at one year

Secondary Outcomes: Frequency of need for subsequent invasive coronary angiography, medical management changes, length of hospital stay, reports of clinician diagnostic certainty

METHODS (BRIEF DESCRIPTION):

- 1,748 patients were enrolled for this study.
- Patient demographics: Mean age 62 years old, 64% male, mean GRACE score of 115, 23% GRACE score >140
- Patients were randomized to either standard of care plus CTCA or standard of care alone.
- ECG gated calcium score and contrast enhanced CTCA were conducted with ≥64 slice scanners. Techniques were used to reduce radiation and heart rate and to use sub-lingual glyceryl trinitrate.
- CTCA's were reported according to the Society of Cardiovascular CT guidelines and the American Heart Association coronary artery segment mode.
- An independent clinical endpoint committee, blinded to the trial intervention, adjudicated the trial's primary outcomes.

INTERVENTION (# IN THE GROUP): 877
COMPARISON (# IN THE GROUP): 871

FOLLOW UP PERIOD: One year

RESULTS:

Primary Outcomes –

- Early CTCA did not improve all-cause mortality or non-fatal myocardial infarction (type 1 or 4b) at one year compared to standard of care (5.8% vs 6.1%, respectively; *P*=.65).

Secondary Outcomes –

- Fewer participants in the CTCA arm received invasive coronary angiography compared to the standard of care arm (54% vs 61%, respectively; *P*=.001).
- Prescription for preventive treatments was similar in both groups (63% vs 62%, respectively; *P*=.52).
- Length of hospital stay was longer in CTCA arm (2.2 vs 2.0, respectively; *P*=.009).
- Clinician reported increased diagnostic certainty after CTCA (mean increase of 1.4; 0-10 scale with 10 being most certain).

LIMITATIONS:

- Open trials have the potential for bias.
- Longer term follow-up might identify further benefits in outcomes.

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The Difference in Transmission of Alpha and Delta Variants After COVID-19 Vaccination

Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants

Eyre DW, Taylor D, Purver M, et al. Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants. *N Engl J Med*. 2022; 386(8):744–756. doi:10.1056/NEJMoa2116597

KEY TAKEAWAY: Vaccination protects against the alpha variant of COVID-19.

STUDY DESIGN: Retrospective observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: COVID-19 vaccination reduced transmission of SARS-CoV-2 from vaccinated persons who became infected, potentially by reducing viral loads, for those infected with the alpha variant. Similar viral loads in vaccinated and unvaccinated persons who are infected with the delta variant call into question the degree to which vaccination prevents transmission.

PATIENTS: Adults in England recently in contact with a positive COVID-19 patient

INTERVENTION: No SARS-CoV-2 infection

CONTROL: SARS-CoV-2 infection

PRIMARY OUTCOME: Vaccination's influence on infection

METHODS (BRIEF DESCRIPTION):

- Used contact-testing data from England to perform a retrospective observational cohort study involving adult contacts of SARS-CoV-2–infected adult index patients.
- PCR testing 1 to 10 days after the index patient had a positive PCR test between January 2 and August 2, 2021.
- Used multivariable Poisson regression to investigate associations between transmission and the vaccination status of index patients and contacts and to determine how these associations varied with the B.1.1.7 (alpha) and delta variants and time since the second vaccination.

INTERVENTION (# IN THE GROUP): 54,667

COMPARISON (# IN THE GROUP): 91,576

FOLLOW UP PERIOD: Not applicable

RESULTS:

- Vaccinated patients exposed to the alpha variant of SARS-CoV-2 were less likely to become infected than unvaccinated peers.
  - BNT162b2: adjusted rate ratio [ARR] 0.32 (95% CI, 0.21–0.48)
  - ChAdOx1 nCoV-19: ARR 0.48 (95% CI, 0.30–0.78)
- Reductions in transmission of the delta variant after two BNT162b2 vaccinations were greater than after two ChAdOx1 nCoV-19 vaccinations.
  - BNT162b2: ARR 0.50 (95% CI, 0.39–0.65)
  - ChAdOx1 nCoV-19: ARR 0.76 (95% CI, 0.70–0.82)

LIMITATIONS:

- Only contacts who had undergone PCR testing were included in the study, therefore the absolute protective effects of vaccination on transmission may be underestimated because vaccine-protected, uninfected contacts may not have sought testing.
- Some contacts may have been infected by a source other than the identified "index patient".
- Did not have sufficient data to account for previous infection status.

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