GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Use Cup Feeding Instead of Bottle Feeding in Preterm Infants to Promote Breastfeeding Success

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GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Avoidance of Bottles During the Establishment of Breastfeeds in Preterm Infants

Allen E, Rumbold AR, Keir A, Collins CT, Gillis J, Suganuma H. Avoidance of bottles during the establishment of breastfeeds in preterm infants. *Cochrane Database Syst Rev.* 2021;10(10):CD005252. Published 2021 Oct 21. doi:10.1002/14651858.CD005252.pub5

KEY TAKEAWAY: In preterm infants who require nutritional supplementation, using cup feeding and avoiding bottle feeding may increase total amount of breastfeeding.
STUDY DESIGN: Meta-analysis of 7 RCTs (N=1,152)
LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: According to the Center for Disease Control and Prevention (CDC), breastfeeding is associated with decreased infant risk of sudden infant death syndrome (SIDS), necrotizing enterocolitis, asthma, obesity, type 1 diabetes, respiratory and gastrointestinal infections, and otitis media as well as decreased maternal risk of breast & ovarian cancer, hypertension and type 2 diabetes. Up to 80% of preterm infants admitted to the NICU experience feeding difficulties due to central nervous system immaturity and are unable to exclusively breastfeed. Prior reviews conveyed mixed results but concluded that cup feeding may have some benefits for late preterm infants, therefore a more robust systematic review and meta-analysis was necessary.

PATIENTS: Preterm infants
INTERVENTION: Cup- or tube-feeding
CONTROL: Bottle-feeding
PRIMARY OUTCOME: Breastfeeding rates
Secondary Outcomes: Time to reach full feeds, duration/volume of feeds, length of hospital stay, weight gain, infection rates, feeding satisfaction

METHODS (BRIEF DESCRIPTION):

- RCTs were extracted from MEDLINE, CENTRAL, CINAHL, and ISRCTN trial registry.
- Inclusion criteria: nutritional supplementation in preterm infants (infants born at <37 weeks' gestation; mean 32 weeks) in the hospital.
- Patients across seven trials were included; five studies used cup-feeding, one study used tube-feeding, one study used novel teat (artificial teat that releases milk with baby's suck).
- Included three quasi-RCTs which were randomized but in which stratification occurred based on weight or gestational age.
- Rates of any breastfeeding or exclusively breastfeeding babies were evaluated.
- GRADE approach was used to evaluate certainty of evidence.

INTERVENTION (# IN THE GROUP): 571
COMPARISON (# IN THE GROUP): 581

FOLLOW UP PERIOD: Six months

RESULTS:
Primary Outcomes –

- Preterm babies in whom bottles were avoided when non-breast supplementation was required in the hospital had higher rates of breastfeeding at all measured intervals:
  - Exclusively breastfeeding upon discharge (6 studies, N=1,074; RR 1.5; 95% CI, 1.2–1.8).
  - Exclusively breastfeeding at six months (three studies, N=887; RR 1.6; 95% CI, 1.1–2.4).
  - Any breastfeeding upon discharge (6 studies, N=1,138; RR 1.1; 95% CI, 1.1–1.2).
  - Any breastfeeding at six months (3 studies, N=886; RR 1.3; 95% CI, 1.1–1.4).

Secondary Outcomes –

- Time to reach full sucking feeds was not faster in the bottles avoided group (3 studies, N=429; MD 2.6 days; 95% CI, –7.2 to 12).
- Length of hospital stay was not shorter in the bottles avoided group (4 studies, N=1,004; MD 2.3 days; 95% CI, –3.4 to 7.9).
- Duration in minutes of supplementary feeds no different between groups (2 studies, N=600; MD –0.42, 95% CI, –2.0–1.1).
- Mean rate of weight gain (3 studies, subtotals only, meta-analysis not possible) one trial showed less weight gain in in the bottle avoided group (MD –186 g; 95% CI, –317 to –56).
- Rate of neonatal infection was no different between groups.
- Parent & Professional satisfaction (1 study, high rate of non-compliance, 85/151, 56% introduced bottles).

LIMITATIONS:

- Sample size was small or moderate for all studies.

- Only one out of seven studies evaluated tube-feeding and the tube-feeding study was of poor quality.
- Low certainty of evidence (low to moderate).
- Rates of breastfeeding, in addition to the intervention, are impacted by factors such as parent commitment, anatomy, education, and access to consultant.

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Patients On Stable, High-Dose Opioid Therapy May Be Harmed by Tapering

Association of Dose Tapering with Overdose or Mental Health Crisis Among Patients Prescribed Long-Term Opioids

Agnoli A, Xing G, Tancredi DJ, Magnan E, Jerant A, Fenton JJ. Association of Dose Tapering with Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids [published correction appears in *JAMA*. 2022 Feb 15;327(7):688] [published correction appears in *JAMA*. 2022 Feb 15;327(7):687]. *JAMA*. 2021;326(5):411-419. doi:10.1001/jama.2021.11013

KEY TAKEAWAY: Decreasing patients' chronic, stable, high-dose opioid therapy may be associated with harm, specifically overdose, withdrawal, hospitalizations for depression, anxiety, and suicide attempts.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Opioid prescribing habits have changed with opioid-related morbidity and mortality. This has led to the implementation of dose reduction strategies to reduce harm associated with opioid use. Despite these changes, clinical guidelines for opioid tapering are limited and may carry risk. This study aims to assess whether there are associations between tapering and adverse events.

PATIENTS: Adults with opioid prescriptions

INTERVENTION: Opioid tapering

CONTROL: No tapering

PRIMARY OUTCOME: Drug overdose/withdrawal and mental health crisis

Secondary Outcomes: Depression, anxiety, and suicide attempt hospitalizations

METHODS (BRIEF DESCRIPTION):

- OptumLabs Data Warehouse was searched for adults who were insured, prescribed opioids ≥ 50 morphine milligram equivalents (MME) per day for greater than one year on stable dose with 14 month follow up between 1/1/2008 – 12/31/2019. Exclusions included death, enrollment disruption, development of cancer, entering hospice/palliative/skilled nursing, and those prescribed buprenorphine.
    - Approximately 70% of patients were >50 years old, most of whom lived in a metropolitan area, and 15% had concurrent substance use disorder.
    - Approximately 25% of patients represented each of the following dose ranges: 50-<90 MME/d, 90->150 MME/d, and 150-<300 MME/d.
- Tapering was identified by a reduction in mean MME ≥15% from baseline dose over 60-day periods of time.
- Two co-primary outcomes measured were overdose/withdrawal events and mental health crisis events.
    - Overdose or withdrawal events were defined as ED visits or inpatient hospital admissions for any drug overdose, alcohol intoxication, or drug withdrawal.
    - Mental health crisis events were defined as Emergency Department (ED) or inpatient hospital admissions with depression or anxiety diagnosis codes or suicide attempt or intentional self-harm.
- Secondary outcomes were ED visit or hospital admission for depression, anxiety, or suicide attempt.
- Covariates (age, sex, level of education, rurality of address, insurance status, baseline mental health, concomitant benzodiazepine use, etc.) were included in the analysis to determine if they contributed to outcomes.

INTERVENTION (# IN THE GROUP): 29,101 (37,170 total person years)

COMPARISON (# IN THE GROUP): 84,517 (166,750 total person years)

FOLLOW UP PERIOD: 12 months

RESULTS:

Primary Outcomes –

- Tapering was associated with more overdose events than non-tapering (adjusted incidence rate difference 1.4 per 100 person-years; 95% CI, 0.7–2.1).
- Tapering was associated with more mental health crisis events than non-tapering (adjusted incidence rate difference 3.1 per 100 person-years; 95% CI, 2.1–4.1).

Secondary Outcomes –

- Tapering was associated with more hospitalizations due to depression than non-tapering (adjusted incidence rate difference 2.5 per 100 person-years; 95% CI, 1.6–3.2).
- Tapering was associated with more hospitalizations due to anxiety than non-tapering (adjusted incidence rate difference 0.4 per 100 person-years; 95% CI, 0.1–

0.7).

- Tapering was associated with more hospitalizations due to suicide attempts than non-tapering (adjusted incidence rate difference 0.2 per 100 person-years; 95% CI, 0.1–0.3).

LIMITATIONS:

- Confounding variables may have increased the risk for adverse events in the tapered population.
- The study did not account for subsequent dose adjustments.
- No accurate measure of race/ethnicity.
- Study did not account for elicit opioid use or methadone.
- Uncertain generalizability as population was insured commercially or via Medicare advantage.

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Using Early Time-Restricted Fasting: A Tool to Consider in the Obese

Effectiveness of Early Time-Restricted Eating for Weight Loss, Fat Loss, and Cardiometabolic Health in Adults with Obesity: A Randomized Clinical Trial

Jamshed H, Steger FL, Bryan DR, et al. Effectiveness of Early Time-Restricted Eating for Weight Loss, Fat Loss, and Cardiometabolic Health in Adults with Obesity: A Randomized Clinical Trial. *JAMA Intern Med*. 2022;182(9):953-962. doi:10.1001/jamainternmed.2022.3050

KEY TAKEAWAY: Early time-restricted eating may be more effective in losing weight and improving mood than eating in a 12 or more-hour window for some obese patients.

STUDY DESIGN: Randomized, unblinded, parallel-arm, clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Time restricted eating (TRE) is a form of intermittent fasting (IF) where eating is constrained to a ten hour or less eating window, and Early Time-Restricted Eating (eTRE) is a form where eating is restricted towards the earlier hours. Studies have shown evidence of some metabolic rhythms, such as insulin sensitivity, to peak in the earlier hours. Previous studies on TRE and IF have been mixed.

PATIENTS: Non-diabetic obese adults seeking weight loss

INTERVENTION: Energy restriction weight loss treatment (ER) and eTRE

CONTROL: ER and Control eating (CON)

PRIMARY OUTCOME: Weight loss and fat loss

Secondary Outcomes: Blood pressure, insulin levels, plasma lipid levels, satisfaction with eating windows, and mood

METHODS (BRIEF DESCRIPTION):

- Patients (25-75 years old) with obesity (BMI 30-60) and without diabetes or unstable medical conditions were included.
- Participants were randomized with stratification by sex, race, and baseline physical activity.
- Those in the eTRE group were restricted to an eating window of 8 hours from 7:00 to 15:00, while the CON group were restricted to 12 or more hours.
- Both groups were instructed to follow their eating window at least 6 days a week, and received weight-loss counseling with ER, dietician counseling, and classes on diet and exercise.
- Body weight was monitored at the beginning and end (fasting) and at two-week intervals (non-fasting) during the trial.
- DEXA scan was used to calculate fat loss.
- Cardiometabolic factors were measured at fasting state.
- Satisfaction with the eating window was measured using five-point Likert scale with higher scores indicating greater satisfaction.
- Mood was measured with the Profile of Mood States-Short Form (POMS-SF) questionnaire, which measures 37 mood states on a five-point scale, with higher scores indicating greater mood disturbances.
- All analyses for this study were intention-to-treat except questionnaire data and the ratio of fat loss to weight loss, where only data from completers of the whole study were included.

INTERVENTION (# IN THE GROUP): 45

COMPARISON (# IN THE GROUP): 45

FOLLOW UP PERIOD: 14 weeks

RESULTS:

Primary Outcomes –

- eTRE resulted in a loss of an additional 2.3 kg of body weight compared to CON (95% CI, –3.7 to –0.9 kg).
- The following results were only reported for completers of the trial:
  - There was no statistically significant difference in absolute fat loss in the eTRE group compared to the CON group (mean difference –1.8 kg; 95% CI, –3.6 to 0).
  - eTRE resulted in greater trunk fat loss than CON (–1.2 kg; 95% CI, –2.2 to –0.1 kg).

Secondary Outcomes –

- There was no significant difference in systolic blood pressure, diastolic blood pressure, insulin levels, plasma lipid levels, or satisfaction between eating windows between the eTRE and CON groups.
- eTRE was more effective at improving mood than CON (–1.7; 95% CI, –3.1 to –0.2).

LIMITATIONS:

- The patient population was primarily women at 80%, limiting generalizability.
- The study had a limited sample size.
- The duration of the study was only 14 weeks.

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Should HPV Vaccination Status Change Management of Abnormal Cervical Cancer Screening Results?

Human Papillomavirus Vaccination History and Diagnosis of Cervical Intraepithelial Neoplasia Grade ≥2 Severe Lesions Among a Cohort of Women Who Underwent Colposcopy in Kaiser Permanente Southern California

Lonky NM, Xu L, Da Silva DM, Felix JC, Chao C. Human papillomavirus vaccination history and diagnosis of cervical intraepithelial neoplasia grade ≥2 severe lesions among a cohort of women who underwent colposcopy in Kaiser Permanente Southern California. *Am J Obstet Gynecol*. 2021;225(6):656.e1-656.e11. doi:10.1016/j.ajog.2021.07.006

KEY TAKEAWAY: Among high-risk women with abnormal cervical cancer results, HPV vaccination status did not change their risk for having a diagnosis of cervical intraepithelial neoplasia grade 2 or higher.
STUDY DESIGN: Retrospective cohort study
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Cervical lesions positive for HPV 16 and 18 have a higher risk of progression and persistence than cervical lesions free of those subtypes. It may be reasonable to assume that women who develop lesions after a history of vaccination for HPV 16 and 18 have a lower likelihood of having CIN grade 2 or higher. Currently, USPSTF guidelines are the same for evaluation of women who have received HPV vaccine and those who have not. This study evaluated whether HPV vaccine status should impact handling of abnormal cervical cancer screening results.

PATIENTS: Women eligible for HPV vaccination who underwent colposcopy and received a pathology diagnosis
INTERVENTION: Prior HPV vaccination
CONTROL: No prior HPV vaccination
PRIMARY OUTCOME: Cervical intraepithelial neoplasm grade 2 or higher

METHODS (BRIEF DESCRIPTION):

- KPSC Orange County Service Area's outpatient colposcopy registry was used to identify patients who had at least one colposcopy between 07/2017 and 08/2018, were between 21 and 38 years old at the time of colposcopy and had a pathology diagnosis on file.
- Data on patient characteristics including sexual history, HPV vaccination history, smoking status, cervical screening and treatment history was obtained from both the registry and KPSC's electronic medical record.
- Original diagnostic slides with CIN2+ diagnosis was obtained from the KPSC Orange County Pathology Center and re-reviewed by study pathologist, who was blinded to the original diagnosis; when re-review suggested a diagnosis other than CIN2+, the sample was considered CIN2 if a p16 biomarker staining result was available and positive.
- CIN2+ lesions were further divided into positive HPV16/18 genotype vs non-HPV16/18 type via HPV genotyping.
- Authors also evaluated whether subdividing the interventions into vaccinations received prior to sexual debut, prior to age 18 and completed series impacted the likelihood of having the primary or secondary outcome.
- Bivariate logistic regressions were used to calculate associations between all variables studied.
- Regression models were adjusted for age, race and ethnicity, smoking status, parity and referral reason.

INTERVENTION (# IN THE GROUP): 311
COMPARISON (# IN THE GROUP): 326

FOLLOW UP PERIOD: Not available

RESULTS:
Primary Outcome –

- There was no association between HPV vaccination history and lower likelihood of CIN2+ diagnosis (adjusted odds ratio [aOR] 1.1; 95% CI, 0.70–1.6).

Secondary Outcomes –

- HPV vaccination was not associated with lower likelihood of HPV 16 or 18 positive CIN2+ (aOR O.78; 95% CI ,0.42–1.5).
- HPV vaccination before sexual debut not associated with lower likelihood of CIN2+ diagnosis (aOR 1.1; CI, 0.55–2.2).
- HPV vaccination series completion not associated with lower likelihood of CIN2+ diagnosis (aOR 0.84, CI, 0.53–1.4).
- First dose of HPV vaccination prior to age 18 was not associated with lower likelihood of CIN2+ diagnosis (aOR 0.96 CI, 0.49–1.9).

LIMITATIONS:

- 66% percent of women were vaccinated after age 18; sample sizes for those age <18 and for other studied

subgroups may not have been large enough to identify differences in outcomes.

- Potential recall bias for approximately 15% of vaccination group whose vaccination history was self-reported.
- Sexual debut was also self-reported and subject to recall bias; additionally, patient interpretation of "sexual debut" has been shown to be variable and may not include all type of sexual contact that places women at risk for HPV exposure.
- Other types of exposure to HPV such as sexual abuse before sexual debut or vertical maternal-fetal transmission were not identified.
- Vaccination history may have affected patient adherence with completing recommended colposcopy.
- Non-Hispanic Black patient subgroup was small, and results may not apply to this group.

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