GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

Pit of Despair? Oxytocin and Postpartum Depression

Not Just for Muscle?

How Whey Protein Supplementation Can Aid Cardiometabolic Health

Pumping Iron in Pregnancy:

Resistance Training Improves Pregnancy Outcomes

Buprenorphine:

A Pain Free Promise or Not Worth the Hype?

FPIN
Family Physicians Inquiries Network

Volume 6 Issue 10

Pit of Despair? Oxytocin and Postpartum Depression

Oxytocin and Postpartum Depression: A Systematic Review

Thul TA, Corwin EJ, Carlson NS, Brennan PA, Young LJ. Oxytocin and postpartum depression: A systematic review. *Psychoneuroendocrinology*. 2020;120:104793. doi:10.1016/j.psyneuen.2020.104793

KEY TAKEAWAY: Endogenous oxytocin levels may be inversely associated with the incidence of postpartum depression (PPD) in patients within one year of delivery. It is unclear if the administration of synthetic oxytocin impacts the incidence of PPD.

STUDY DESIGN: Systematic review of 16 cohort studies (N=50,225)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to lack of statistical analysis)

BRIEF BACKGROUND INFORMATION: PPD is a common concern and results in significant morbidity following delivery. Oxytocin is an endogenous hormone which increases during pregnancy and following delivery. Synthetic oxytocin is a common intervention used to induce or augment labor and prevent or treat postpartum hemorrhage. The study aimed to investigate the association between endogenous oxytocin levels and exogenous oxytocin exposure and the incidence of PPD.

PATIENTS: Patients within one year of delivery

INTERVENTION: Measurement of endogenous oxytocin; administration of exogeneous oxytocin

CONTROL: Standard of care; patients not receiving synthetic oxytocin

PRIMARY OUTCOME: PPD symptoms and endogenous oxytocin levels

METHODS (BRIEF DESCRIPTION):

- Database searches included PPD or postnatal depression and oxytocin, synthetic oxytocin, syntocinon, Duratocin, Pitocin.
  - Abstracts without full peer review, theoretical articles, review or meta-analysis articles, and case studies were excluded.
  - Exclusively prenatal studies and studies >1 year postpartum were also excluded.
- Studies were critically assessed using the Newcastle-Ottawa quality assessment scale and high-quality studies were included.
- Individuals in the first year postpartum were assessed for incidence of PPD.
- Two arms of the study were assessed:
  - 12 studies assessed endogenous oxytocin levels
  - Four studies assessed exposure to synthetic oxytocin in the peripartum period
- Individuals assessed for endogenous oxytocin were compared within the group.
- Individuals with synthetic oxytocin exposure were compared to those without exposure.
- Various standardized measurements of PPD were used, including Edinburgh Postnatal Depression Score (EPDS) and Blues questionnaire, as well as clinical diagnoses were used to measure the primary outcome.
- Endogenous oxytocin levels were measured via various methods using both serum and urine samples.

INTERVENTION (# IN THE GROUP):

- Endogenous oxytocin: 2,435
- Synthetic oxytocin: 47,790

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable (up to 1 year postpartum)

RESULTS:

Primary Outcome –

- Endogenous arm:
  - Eight studies demonstrated an inverse association between oxytocin levels and depression symptoms, two found no significant relationship, and one found a positive association (no statistical analysis completed).
  - One study noted an association between change in oxytocin level trajectory but not with the absolute oxytocin value (no statistical analysis completed).
- Synthetic oxytocin arm:
  - Two studies found a negative association between oxytocin administration and postpartum depression, one found no effect, and one found a positive association (no statistical analysis completed).

LIMITATIONS:

- Due to the small number of studies, a meta-analysis was not performed.
- Studies used a variety of methods to define PPD, limiting comparability.
- Some studies assessed breastfeeding status as a known confounder, but not all.

John Rambo, MD
Northwest Washington FMRP
Bremerton, WA

Not Just for Muscle? How Whey Protein Supplementation Can Aid Cardiometabolic Health

The Effects of Whey Protein Supplementation on Indices of Cardiometabolic Health: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Prokopidis K, Morgan PT, Veronese N, et al. The Effects of Whey Protein Supplementation on Indices of Cardiometabolic Health: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Clin Nutr*. 2025;44:109-121. doi:10.1016/j.clnu.2024.12.003

KEY TAKEAWAY: Supplementation with whey protein for at least four weeks is associated with a reduction in total cholesterol in adults, especially in adults <50 years old and when combined with exercise.

STUDY DESIGN: Systematic review and meta-analysis of 21 randomized controlled trials (RCTs) (N=3,617)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small sample sizes and high heterogeneity of interventions)

BRIEF BACKGROUND INFORMATION: Cardiometabolic risk factors play major roles in the onset of type 2 diabetes and cardiovascular disease. One of the most important ways to improve one's cardiometabolic profile is through dietary modification. As dietary protein is involved in multiple mechanisms of metabolic health, this study aimed to explore the effects of whey protein supplementation on various markers of cardiometabolic health.

PATIENTS: Adults regardless of health status

INTERVENTION: Whey protein supplementation for at least four weeks

CONTROL: Carbohydrate or placebo (i.e., maltodextrin)

PRIMARY OUTCOME: Cardiometabolic outcomes

Secondary Outcome: Sub-group analysis of primary outcome

METHODS (BRIEF DESCRIPTION):

- A systematic search was performed for RCTs in which participants were >18 years old, the intervention group received whey protein supplementation for at least four weeks, and the control group received either carbohydrates or placebo.
- The following cardiometabolic outcomes were used in the analysis:
  - Systolic blood pressure (SBP)
  - Diastolic blood pressure (DBP)
  - High-density lipoprotein-cholesterol (HDL-cholesterol)
  - Low-density lipoprotein-cholesterol (LDL-cholesterol)
  - Total cholesterol
  - The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index
- The difference in cardiometabolic outcomes between groups was measured by comparing blood pressure, lipoprotein profile, and glycemic control.
- Subgroup analysis was performed to evaluate other statistically significant differences between age, treatment duration, added exercise, whey protein dose, body mass index, and placebo vs non-placebo.
- P-value <0.05 was statistically significant.

INTERVENTION (# IN THE GROUP):

- BP: 326
- HDL: 300
- LDL: 291
- Total cholesterol: 300
- Triglycerides: 327
- HOMA-IR: 171

COMPARISON (# IN THE GROUP):

- BP: 371
- HDL: 327
- LDL: 318
- Total cholesterol: 327
- Triglycerides: 327
- HOMA-IR: 232

FOLLOW-UP PERIOD: At least four weeks

RESULTS:

Primary Outcome –

- Whey protein supplementation lowered total cholesterol compared to control (13 trials, n=327; mean difference [MD] –6.4; 95% CI, –11 to –1.7; I^2=71%).
- Whey protein supplementation did not show significant effects on blood pressure, HDL-cholesterol, LDL-cholesterol, triglyceride concentration, HOMA-IR index, compared to control.
  - SBP (12 trials, n=371; MD –1.5; 95% CI, –3.5 to 0.47; I^2=76%)

- DBP (12 trials, n=371; MD –1.1, 95% CI, –2.6 to 0.49; I^2=81%)
- HDL-cholesterol (13 trials, n=327; MD –0.82; 95% CI, –2.2 to 0.53; I^2=43%)
- LDL-cholesterol (12 trials, n=318; MD –2.1; 95% CI, –4.1 to –0.03; I^2=6%)
- Triglyceride concentration (13 trials, n=327; MD –3.2; 95% CI, –8.0 to 1.6; I^2=78%)
- HOMA-IR (8 trials, n=232; MD 0.24; 95% CI, –0.27 to 0.76; I^2=82%)

Secondary Outcome –

- Through subgroup analysis, whey protein supplementation showed statistically significant effects in the following, compared to control:
  - LDL-cholesterol decreased in individuals aged <50 years (6 trials; MD –4.8; 95% CI, –8.3 to –1.2; I^2=0%) with whey protein combined with exercise (8 trials; MD –5.4; 95% CI, –8.9 to –1.9; I^2=0%).
  - Total cholesterol decreased in several subgroups:
    - <50 years (7 trials; MD –8.2; 95% CI, –15.0 to –1.3; I^2=68%)
    - >50 years (6 trials; MD –5.9; 95% CI, –7.7 to –4.0; I^2=0%)
    - BMI >25 kg/m2 (11 trials; MD –6.7; 95% CI, –12 to –1.8; I^2=74%)
    - Treatment dose >35 g/d (7 trials; MD –5.6; 95% CI, –7.5 to –3.8; I^2=0%) and dose <35 g/d (6 trials; MD –12; 95% CI, –18 to –6.7; I^2=41%)
    - Non-placebo control (4 trials; MD –7.5; 95% CI, –15 to –0.40; I^2=88%)
    - Whey protein combined with exercise (9 trials; MD –8.6; 95% CI, –14 to –2.8; I^2=55%)

LIMITATIONS:

- The sample size of each study was small.
- Only five of the studies were conducted in the United States, and thus the findings may not be generalizable to the US population.
- There was high heterogeneity between studies.
- Differences in dose and duration of whey protein supplementation.
- Some incorporated exercise which also varied in type.
- Different countries may have variable formulations of whey protein.

Anthony Pech, DO
Kadlec Regional Medical Center Program
Richland, WA

Pumping Iron in Pregnancy: Resistance Training Improves Pregnancy Outcomes

Resistance Training in Pregnancy: Systematic Review and Meta-Analysis of Pregnancy, Delivery, Fetal and Pelvic Floor Outcomes and Call to Action

Prevett C, Gingerich J, Sivak A, Davenport MH. Resistance Training in Pregnancy: Systematic Review and Meta-analysis of Pregnancy, Delivery, Fetal and Pelvic Floor Outcomes and Call to Action. *Br J Sports Med*. 2025;59(16):1173-1182. Published 2025 Jul 31. doi:10.1136/bjsports-2024-109123

KEY TAKEAWAY: Resistance training (RT) during pregnancy, either alone or as part of a multimodal fitness regimen, appears to reduce the risk of developing gestational hypertension (GHTN), gestational diabetes (GDM), perinatal mood disorders, and macrosomia.

STUDY DESIGN: Systematic review and meta-analysis 45 randomized controlled trials (RCTS), three non-RCTs, and two cohort studies (N=47,619)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to intervention variability)

BRIEF BACKGROUND INFORMATION: Studies have shown that physical activity during pregnancy decreases the risk of GDM, preeclampsia, and cesarean birth. However, much of the obstetric data primarily examines the benefits of aerobic exercise. This study aimed to investigate whether RT, which has been shown to reduce all-cause mortality in the general population, also improves pregnancy outcomes.

PATIENTS: Pregnant individuals

INTERVENTION: RT

CONTROL: No RT

PRIMARY OUTCOME: Rates of pregnancy-induced hypertension, GDM, perinatal mood disorders
Secondary Outcome: Delivery-related events, fetal outcomes, pelvic floor-related conditions

METHODS (BRIEF DESCRIPTION):

- Six databases were searched with dates ranging from inception to March 15, 2024 to obtain studies examining RT of any intensity during pregnancy compared with either routine pregnancy care or non-RT, resulting in 50 studies (44 included, 6 described narratively) from 14 countries.
- Eligible studies included patients at any gestational age without any gestational complications at baseline. Pilates and yoga were excluded.
- Most studies (45) were multicomponent (aerobic exercise + RT) with low to moderate intensity RT completed 2–4 times a week.
- RT was defined as at least four weeks of RT using an external load (e.g. free weights, weight machines, resistance bands) alone or as part of a multimodal exercise regimen.
- Control groups in the RCTs were either no exercise/intervention, online intervention/education only, or different exercise types (e.g. low-intensity or aerobic exercise).
- Control groups in the non-RCTs were different exercise types, exercise frequency, or exercise behavior.
- The primary outcomes included the rate of pregnancy-induced hypertension disorders (i.e. GHTN or pre-eclampsia), GDM, and perinatal mood disorders (i.e. anxiety or depression during pregnancy or postpartum).
- Secondary outcomes included:
  - Delivery-related events (caesarean delivery rate, instrumental delivery, premature delivery, perineal tear)
  - Fetal outcomes (rates of macro or microsomia, gestational age at delivery)
  - Pelvic floor-related conditions (urinary incontinence, pelvic organ prolapse, pelvic pain, diastasis recti)
- A random-effects model was used to conduct a meta-analysis. I^2 was used to assess study heterogeneity.
- The Johanna Briggs Institute (JBI) critical appraisal tool was used to assess study bias.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- RT was associated with a lower risk of GHTN compared to non-RT (7 studies, n=2,413; odds ratios [OR] 0.42; 95% CI, 0.27–0.66; I^2=0%).

- There was no difference in pre-eclampsia rates between RT and non-RT (4 studies, n=1,681; OR 0.74; 95% CI, 0.40–1.4; I^2=35%).
- RT was associated with a lower risk of GDM compared to non-RT (16 studies, n=4,712; OR 0.62; 95% CI, 0.48–0.79; I^2=0%).
- RT was associated with a lower the risk of perinatal mood disorders compared to non-RT (5 studies, n=1,602; OR 0.48; 95% CI, 0.32–0.73; I^2=0%).

Secondary Outcome –

- There was no significant difference between RT and non-RT in caesarean delivery rates, instrumental delivery rate, perineal tearing, preterm delivery, or microsomia.
- RT demonstrated a reduced rate of macrosomia compared to the control (19 studies, n=not available; OR 0.67; 95% CI, 0.50–0.88; I^2=23%).
- There was insufficient data to analyze pelvic floor outcomes.

LIMITATIONS:

- RT was included as part of a multimodal exercise regimen rather than a sole intervention in 90% of the included studies, limiting this study's ability to directly evaluate the role of RT alone on pregnancy outcome.
- Included studies did not clearly delineate the intensity of resistance training completed, making it difficult to assess the impact of specific loading schemes (low, moderate, high intensity) during pregnancy.
- There was significant variability in control groups definitions.
- Sixteen studies had low bias risk (≥70% of assessment criteria were affirmative), 27 had moderate bias risk (50–69% of assessment criteria were affirmative), and seven had high bias risk (≥50% of assessment criteria were affirmative).

Robert Goldin, MD
Naval Medical Center Camp Lejeune FMRP
Camp Lejeune, NC

Buprenorphine: A Pain Free Promise or Not Worth the Hype?

Buprenorphine, Pain, and Opioid Use in Patients Taking High-Dose Long-Term Opioids: A Randomized Clinical Trial

Becker WC, Seal KH, Nelson DB, et al. Buprenorphine, Pain, and Opioid Use in Patients Taking High-Dose Long-Term Opioids: A Randomized Clinical Trial. *JAMA Intern Med*. 2025;185(4):372-381. doi:10.1001/jamainternmed.2024.8361

KEY TAKEAWAY: Patients with chronic pain on opioid therapy given the option to switch to buprenorphine do not report improved pain levels and greater reductions in opioid dosage compared to patients on opioid taper alone.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to low number of study participants electing to switch to intervention)

BRIEF BACKGROUND INFORMATION: Patients receiving long-term, high dose opioid therapy for pain are at high risk for physical dependence. Guidelines recommend utilizing an opioid taper for patient safety, but physical dependence can be a barrier to successfully decreasing opioid medication. Buprenorphine has been touted as an alternative to tapering long-term opioid therapy, but strategies on how to utilize this have been limited. The aim of this study was to assess if patients receiving the option of buprenorphine therapy reported lower levels of pain and greater reductions of opioid dosage compared to patients not receiving this option.

PATIENTS: Adults with chronic pain on opioids

INTERVENTION: Buprenorphine treatment

CONTROL: No buprenorphine

PRIMARY OUTCOME: Pain severity

Secondary Outcome: Opioid dose

METHODS (BRIEF DESCRIPTION):

- Veterans Affairs (VA) patients (89% male, average age of 60 years old) with moderate-to-severe pain despite treatment with high-dose long term opioid therapy were recruited for the study.
- Patients were recruited from 10 VA sites across the United States.
- Inclusion criteria:
  - Pain nearly every day for ≥6 months, Enjoyment of Life, and General Activity (PEG) 3-item pain score >5. Scores on the PEG range from 0–10, with higher scores indicating worse pain.
  - Qualifying opioid analgesics for >3 consecutive months with an opioid dosage of at least 70 morphine milliequivalent (MME) per day.
- Patients with moderate to severe opioid use disorder and/or currently receiving medication treatment for opioid use disorder were excluded from the study.
- Patients were randomized and blinded to one of the following treatment arms:
  - Providers offered a traditional gradual taper of opioids as tolerated.
  - Providers offered the option to utilize buprenorphine as part of opioid taper protocol.
- Treatments were administered by primary care physicians or advanced practice providers who were not blinded.
- In both treatment arms, clinicians created patient-centered pain management recommendations and collaborated with patients to decrease opioid dosage.
  - Study participants who elected to use buprenorphine therapy as part of their opioid taper were initially prescribed a traditional buprenorphine technique, but this was later changed to have patients start at a subtherapeutic dosage of buprenorphine for up to a week while continuing to take full agonist opioid therapy before transitioning completely to buprenorphine.
- Pain was measured using the Brief Pain Inventory (BPI) score. Scores range from 0–10, with higher scores indicating increased pain.
- Opioid dose in MME was measured at 12 months.
- The average daily MME was measured at three, six, nine, 12, and 15 months post initial intervention.
  - Buprenorphine was not included in MME calculations.

INTERVENTION (# IN THE GROUP): 104

COMPARISON (# IN THE GROUP): 103

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Buprenorphine did not improve pain compared to no buprenorphine at 12 months (adjusted mean difference [AMD] –0.09; 95% CI, –0.52 to 0.34).
    - Buprenorphine baseline BPI (score 6.8; standard deviation [SD] 1.5); BPI at 12 months (score 6.1; SD 1.9)
    - No buprenorphine baseline BPI (score 6.8; SD 1.6); BPI at 12 months (score 6.3; SD 1.7)

Secondary Outcome –

- Buprenorphine had no significant difference in opioid dosage at 12 months compared to no buprenorphine.

LIMITATIONS:

- The study population was largely male and older, which makes results difficult to generalize.
- This study reviewed medications dispensed and not self-reported opioid use.
- There were low rates of switching to buprenorphine in the study (26% of the intervention arm), which makes it difficult to fully assess efficacy of treatment.

Raye Reeder, MD, MPH
University of Oklahoma School of Community Medicine
Tulsa, OK