GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of August 23 - 27, 2021

SPOTLIGHT: The Growing Need for RCTs of Hormone Therapy in Transgender Women

The Growing Need for RCTs of Hormone Therapy in Transgender Women

Antiandrogen or Estradiol Treatment or Both during Hormone Therapy in Transitioning Transgender Women

Haupt C, Henke M, Kutschmar A, et al. Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women. *Cochrane Database Syst Rev*. 2020; 11(11):CD013138. Published 2020 Nov 28. doi:10.1002/14651858.CD013138.pub2

KEY TAKEAWAY: Due to the lack of studies, there is insufficient evidence to determine the efficacy and the safety of hormonal treatment methodologies for transgender women who are transitioning. The lack of evidence reveals the disparity between current medical practice and research.

STUDY DESIGN: Systematic review of RCTs, quasi-RCTs, and controlled-cohort studies

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Gender dysphoria causes significant distress in patients making them want to change their characteristics to be in congruence with their desired gender. Gender dysphoria is presenting more often in clinics. Current treatment includes hormone therapy for transgender women in order to suppress their male characteristics. Because of this, more research is needed in order to study the effects, efficacy, and satisfaction of outcomes regarding hormone therapy.

PATIENTS: Transgender women

INTERVENTION: Antiandrogens and estradiol or antiandrogens alone or estradiol alone

CONTROL: Placebo

OUTCOME: Quality of life, satisfaction with change, adverse events specific to hormone therapy

METHODS (BRIEF DESCRIPTION):

- 787 RCTs were initially screened, in which 13 studies were eligible for the full-text screening stage. Only one ongoing study met the inclusion criteria.
- The study included transgender women at least 16 years old who were in the process of changing their sexual characteristics.
- Only research that evaluated hormone interventions was included.
- Outcomes were measured by validated generic instruments (Quality of Life Inventory) or specific instruments (Body Image Quality of Life Inventory or Sexual Satisfaction Scale for Women). Tools such as the Utrecht Gender Dysphoria Scale were also used.
- Measurements of specific body changes (breast size, skin thickness, skin sebum production, and hair growth) were also measured.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Follow up would have been at three to six months (short-term), six months to two years (medium-term), and more than two years (long-term).

RESULTS: No studies met the inclusion criteria; however, there was one current ongoing RCT study in Thailand. This study compared estradiol valerate plus cyproterone treatment with estradiol valerate plus spironolactone treatment. Testosterone levels were measured after three months (no results to date).

LIMITATIONS: It was not possible to assess for bias or limitations as no studies met the inclusion criteria.

Jody Bahnmiller-Brasil, MD, FAAFP
Northeast Georgia Medical Center FMRP
Gainesville, GA

Levonorgestrel IUD is Equivalent to Copper IUD for Emergency Contraception

Levonorgestrel vs. Copper Intrauterine Devices for Emergency Contraception

Turok DK, Gero A, Simmons RG, et al. Levonorgestrel vs. Copper Intrauterine Devices for Emergency Contraception. *N Engl J Med*. 2021; 384(4):335–344. doi:10.1056/NEJMoa2022141

KEY TAKEAWAY: In patients who desire emergency contraception within five days of unprotected sexual intercourse, levonorgestrel IUD was noninferior to copper IUD in preventing pregnancy.

STUDY DESIGN: Multi-site single blinded randomized noninferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Both copper and levonorgestrel IUDs are known to be effective at preventing pregnancy. No IUD is currently FDA approved for emergency contraception; however, observational studies have shown effectiveness of the copper IUD for this purpose. Of the two oral emergency contraceptives available, levonorgestrel must be taken within 3 days of unprotected intercourse. Previous trials have demonstrated patient preference for levonorgestrel over copper IUDs due to reduced menstrual discomfort and bleeding. No previous studies have directly compared IUDs for emergency contraception.

PATIENTS: Unprotected sexual intercourse within the previous five days and desired emergency contraception

INTERVENTION: Levonorgestrel 52 mg IUD

CONTROL: Copper T380A IUD

OUTCOME: Urine pregnancy test one month after IUD replacement

METHODS (BRIEF DESCRIPTION):

- Participants were English or Spanish speaking women 18–35 years old recruited from six family planning clinics in Utah.
- Inclusion Criteria: Requesting emergency contraception after one or more episodes of unprotected sexual intercourse within the previous five days, desire to initiate IUD, desire to prevent pregnancy for at least one year, negative urine pregnancy test at time of randomization, history of regular menstrual cycles
- Follow up at 30 days with a home and/or in-clinic urine pregnancy test and a survey
    - Follow up surveys at 3 and 6 months

INTERVENTION (# IN THE GROUP): 355

COMPARISON (# IN THE GROUP): 356

FOLLOW UP PERIOD: Data collected for 6 months on outcomes one month after insertion

RESULTS:

Primary Outcome:

- There was no difference in incidence of pregnancy at one month (Incidence Difference 0.3 per 100; 95% CI, –0.9 to 1.8).

Secondary Outcomes:

- One pregnancy occurred in the levonorgestrel group and ended in spontaneous abortion.
- There was less cramping with levonorgestrel vs. copper IUD (Adjusted Mean Difference –10.3; 95% CI –16 to –4.9).
- There were more bleeding days with levonorgestrel vs. copper IUD (Adjusted Mean Difference 3.5; 95% CI, 2.4 to 4.6).
- No difference in rates of expulsion, removal, or participant satisfaction level.

LIMITATIONS:

- 68 participants were lost to one month follow up.
- Clinicians were aware of the IUD type.
- African Americans were underrepresented.
- Potential for selection bias given that only 7% of clinic patients seeking emergency contraception were enrolled in the trial.
- Efficacy of IUD for emergency contraception was not compared with other emergency contraceptive methods.

Ian P. Coe, MD
Montana FMR
Billings, MT

Clinical Academic Careers: The Factors Within

Factors Impacting on Retention, Success, and Equitable Participation in Clinical Academic Careers: A Scoping Review and Meta-Thematic Synthesis

Vassie C, Smith S, Leedham-Green K. Factors impacting on retention, success and equitable participation in clinical academic careers: a scoping review and meta-thematic synthesis. *BMJ Open*. 2020 Mar 25; 10(3):e033480. doi: 10.1136/bmjopen-2019-033480.

KEY TAKEAWAY: Interventions to address the factors affecting equitable participation in clinical academia will have to focus on structural and cultural factors as well as individual needs.

STUDY DESIGN: Scoping review and meta-thematic synthesis

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Clinical academics combine clinical practice with academic research. Teaching and the breadth of skills is important in training the next generation of medical professionals. The declining number of clinical academics, observed internationally, is concerning. Issues with recruitment and retention within clinical academia affect certain demographic groups disproportionately. A diverse clinical academic workforce is not only important from a values perspective, but it also drives innovation and excellence in research and teaching. From an economic perspective, the attrition of a highly trained elite workforce due to potentially remediable factors warrants attention and investment.

PATIENTS: Clinical academics

INTERVENTION: Factors involved in recruiting clinical academics

CONTROL: None

OUTCOME: Retention and success

METHODS (BRIEF DESCRIPTION):

- A scoping review of English language articles between January 2005 and April 2019 published in North America, Australia, and Western Europe on factors influencing recruitment, retention, promotion, and equitable participation was conducted. The most recent and relevant articles were selected for meta-thematic analysis using inclusion and exclusion criteria.
- Qualitative meta-thematic synthesis was done which identified 13 themes organized into personal, interpersonal, organization, and societal categories using a socioecological approach.
- Resulting framework used to describe and explain the subject.

INTERVENTION (# IN THE GROUP): Not applicable

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW UP PERIOD: Not applicable

RESULTS: The broad nature of these factors suggests the interventions will need to address structural and cultural factors as well as individual needs.

- Personal Factors: Social capital, financial considerations, confidence and ambition, orientation to roles, competing demands, and priorities
- Organizational Factors: Academic culture, clinical workplace culture, organizational policies, and practices
- External (Societal) Factors: National clinical academic structures and funding, social attitudes to diversity and equity
- Interpersonal Factors: Supportive factors, discriminatory factors, compensatory behaviors

LIMITATIONS:

- Social class was not included as a search term.
- There is limited literature on equitable participation for ethnic minorities and LGBTQ+ clinicians.
- No papers related to disability in this arena were identified.
- The findings have little relevance to nursing, midwifery, and allied health professionals.

Leslie David, MD
Northeast Georgia Medical Center FMRP
Gainesville, GA

Overweight? Lose Weight Long-Term with Metformin?

Long-Term Weight Loss with Metformin or Lifestyle Intervention in the Diabetes Prevention Program Outcomes Study

Apolzan JW, Venditti EM, Edelstein SL, et al. Long-Term Weight Loss With Metformin or Lifestyle Intervention in the Diabetes Prevention Program Outcomes Study [published correction appears in Ann Intern Med. 2020 Sep 15;173(6):508]. *Ann Intern Med*. 2019; 170(10):682–690. doi:10.7326/M18-1605

KEY TAKEAWAY: Continued metformin use and more initial weight loss (>5%) was predictive of sustained long-term weight loss (LTWL) for obese or overweight patients with glucose intolerance.

STUDY DESIGN: Randomized controlled cohort trial with an unmasked treatment phase

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Type 2 diabetes mellitus (T2DM) is one of the most common diseases seen by family physicians. Metformin has been a staple in the armamentarium of pharmacological therapies targeting T2DM. For its effects on insulin resistance and glycemic control, metformin has widely been considered safe and effective. The Diabetes Prevention Program Outcomes Study (DPPOS) is the longest running diabetes prevention study. This report examines retrospectively the difference in LTW in patients on metformin versus intensive lifestyle treatment or placebo.

PATIENTS: BMI >25 and hyperglycemia with initial first year weight loss >5%

INTERVENTION: Metformin and weight loss monitored for years 2–15

CONTROL: Placebo (lifestyle only)

OUTCOME: Weight loss

METHODS (BRIEF DESCRIPTION):

- Participants in the Diabetes Prevention Program (DPP) trial were initially randomized to three groups: intensive lifestyle modification, metformin (850mg/twice daily), or placebo.
- If HbA1c was ≥7, they were referred to their primary care physician for ongoing diabetes management.
- The DPPOS study is ongoing and at the 15-year mark, the data about long-term weight loss was analyzed.
- Utilized logistic regression models and Generalized Estimating Equation (GEE) models to determine predictive variables.

INTERVENTION (# IN THE GROUP):

- Metformin: 289
- Intensive Lifestyle: 137

COMPARISON (# IN THE GROUP): 137

FOLLOW UP PERIOD: 15 years

RESULTS: Mean weight loss was maintained after year one across all groups.

- Metformin: 6.2% (95% CI, 5.2% to 7.2%).
- Intensive Lifestyle: 3.7% (95% CI, 3.1% to 4.4%).
- Placebo: 2.8% (95% CI, 1.3% to 4.4%).

- Active use of metformin (vs. nonuse) predicted overall long-term weight loss (OR 1.9, *P*<.001)
- Other predictors of long-term weight loss:
  - Greater weight loss in year one
  - Older age and continued metformin use was predictive in the metformin group
  - Older age and not having family or personal history of diabetes in intensive lifestyle group
  - Higher baseline fasting glucose was predictive of more long-term weight loss in the placebo group

LIMITATIONS:

- Post hoc analysis
- Potential for bias during long length and multiple treatment protocols including offering intensive lifestyle treatment for all participants in the year between DPP and DPPOS.
- Lack of an intensive lifestyle + metformin arm as this study showed more initial weight loss with the intensive lifestyle intervention.

Monica Newton, DO, MPH
Northeast Georgia FMRP
Gainesville, GA

Persistent Sciatica: Is Surgery Really the Answer?

Surgery versus Conservative Care for Persistent Sciatica Lasting 4 to 21 Months

Bailey CS, Rasoulinejad P, Taylor D, et al. Surgery versus Conservative Care for Persistent Sciatica Lasting 4 to 12 Months. *N Engl J Med*. 2020; 382(12):1093–1102. doi:10.1056/NEJMoa1912658

KEY TAKEAWAY: For patients with chronic sciatica due to a herniated disk in the lower lumbar spine, surgical management provided slightly better pain relief at 6 months (but not at 12 months) compared to conservative management.
STUDY DESIGN: Randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Sciatica caused by acute disc herniation resolves in 90% of patients with conservative care within four months. Studies of surgery for acute sciatica demonstrate some benefit to surgery over conservative treatment. However, little research exists evaluating surgery vs conservative management in those with chronic sciatica.

PATIENTS: Patients with chronic sciatica of the lumbar spine
INTERVENTION: Surgery
CONTROL: Conservative Management
OUTCOME: Leg pain on the visual analogue scale (VAS) at 6 months
Secondary outcomes: Pain, disability, and function at 6 and 12 months

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: 18–60 years old with history of unilateral radiculopathy for 4 to 12 months, MRI findings of disc at L4-L5 or L5-S1 disk, compression of associated nerve root.
- Conservative management: Education about activity, exercise, oral analgesics, physiotherapy, and epidural steroid injections if desired.
- Surgery: Microdiskectomy
- Outcomes measured at baseline, 6 weeks, and 3, 6, & 12 months:
  - Leg and back pain on the VAS (0–10 cm, higher scores worse symptoms)
  - Disability via the Oswestry Disability Index (0–100 pts, higher scores worse symptoms
  - Function via the SF-36 Physical Component Summary and SF-36 Mental Component Summary (based on normative data, higher scores=better function)
  - Employment status
  - Satisfaction with treatment

INTERVENTION (# IN THE GROUP): 64
COMPARISON (# IN THE GROUP): 64

FOLLOW UP PERIOD: 12 months

RESULTS:

- Leg-pain intensity on the VAS at 6 months was significantly lower in the surgery group vs conservative group (2.8 vs 5.2 cm; difference 2.4 cm; 95% CI, 1.4–3.4).
  - The minimal clinically important difference on the VAS is 1.3 cm.
- The authors report that due to a lack of a plan for adjustment for multiple comparisons, none of the secondary outcomes can be used for any clinical inferences.

LIMITATIONS:

- Single center study limits generalizability.
- Potential for selection bias as those with severe pain possibly less willing to participate in conservative care.
- High crossover rate from nonsurgical to surgical group (34%) threatens validity and 20% of data for primary outcome missing.
- Secondary outcomes not adjusted for multiple comparisons limiting ability to make any clinical inferences.

Curtis J Papenfuss, MD
Family Medicine of Southwest Washington
Vancouver, WA