GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 33

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of August 14 - 18, 2023

SPOTLIGHT: Intrauterine Device (IUD) Insertion Following Medical Abortion Could Be Made More Convenient and Less Painful

- Don't Stress, Refresh: How Physical Exercise Can Benefit Sleep and Stress levels
- Can Mindfulness Meditation Help with Anxiety and Depression in Patients with Insomnia?
- Does Metformin Exposure In-Utero Lead to Increased BMI in Infants?

Intrauterine Device (IUD) Insertion Following Medical Abortion Could Be Made More Convenient and Less Painful

Placement of an Intrauterine Device Within 48 Hours After Early Medical Abortion: A Randomized Controlled Trial

Hogmark S, Liljeblad KL, Envall N, Gemzell-Danielsson K, Kallner HK. Placement of an intrauterine device within 48 hours after early medical abortion-a randomized controlled trial. *Am J Obstet Gynecol*. 2023;228(1):53.e1-53.e9. doi:10.1016/j.ajog.2022.07.063

KEY TAKEAWAY: Early IUD placement following medical termination of pregnancy (TOP) does not lead to higher rates of continued use at six months. However, it is safe, without increased complications, and may result in less pain and increased patient satisfaction.

STUDY DESIGN: Open-label, randomized, controlled, multicenter, superiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Effective contraception can prevent unplanned pregnancy. IUDs are typically inserted two to four weeks following abortion. Women who miss this follow-up could be left without coverage. This study questions if IUD insertion at 48 hours post-abortion could be equivalent or superior to the status quo.

PATIENTS: Women after elective TOP

INTERVENTION: IUD placement within 48 hours

CONTROL: IUD placement at two to four weeks

PRIMARY OUTCOME: Use of IUD at six months post TOP

Secondary Outcome: IUD expulsion rate, pain at placement, patient satisfaction, and complications

METHODS (BRIEF DESCRIPTION):

- 252 women seeking TOP ≥18 years old and ≤63 days gestational age were recruited at five Swedish clinics.
  - 12 declined to participate.
  - Exclusion criteria included contraindications to medical abortion or IUDs.
- 240 women were randomly allocated 1:1 into two groups using permuted blocks of four to eight.
  - Groups were comparable in age, education levels, parity, and gestation.
- After allocation, several participants were excluded from the study for the following reasons:
  - Complicated TOP due to bleeding, infection, or retained products
  - Failure to have their IUD inserted according to study protocol
  - Voluntary withdrawal of consent
  - Loss to follow up.
- Intervention Group (IG): IUD inserted within 48 hours of TOP
- Comparison Group (CG): IUD inserted at two to four weeks after TOP (standard of care)
- Participants were able to select their IUD of choice at no cost (Mirena®, Kyleena®, Jaydess®, NovaT®).
- Pain at insertion was reported using a visual analog scale.
- Participants were contacted at three-, six-, and 12-months post-IUD insertion via phone or email to complete a questionnaire.
  - It aimed to determine study-related sequelae such as IUD expulsion, removal, continued use, pregnancy, adverse events, and satisfaction levels.
- Modified Intention to Treat (mITT) analysis included patients with IUDs inserted outside the study protocol.

INTERVENTION (# IN THE GROUP): 111

COMPARISON (# IN THE GROUP): 112

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- There was no difference in IUD usage rates at sex months post elective abortion between patients who received an IUD at 48 hours vs patients who received it at 2-4 weeks.
  - (82% vs 77%, respectively; difference in proportion; 4.3% 95% CI, –0.062 to 0.15)

Secondary Outcome –

- Self-reported expulsion rates between IG and CG were comparable at six months.
- IG had significantly lower pain scores than CG.
  - IG mean pain score =32 (SD=29) compared with CG mean pain score =43 (SD= 28), *P*=.002.
- Adverse events and complications were minimal but comparable between groups.
  - Seven intrauterine and one ectopic pregnancy

    - Three patients had their IUDs removed due to side effects.
- Patients preferred the timing of IUD placement in the IG (difference in proportion 13.4%; *P*=.03).

LIMITATIONS:

- It was not feasible to blind patients in this RCT.
- The study was powered for the primary outcome, but not rare adverse events.
- Participants only represent a certain subset of women seeking termination of pregnancy and may not be generalizable.
- The study design differs from standard clinical practice and may have influenced patient experiences.
    - Patients do not typically have a choice of free IUDs, nor do they get follow-up appointment scheduling.

Meghan O'Brien, MD
Good Samaritan Family Medicine Residency
Corvallis, OR

Don't Stress, Refresh: How Physical Exercise Can Benefit Sleep and Stress Levels

The Effects of Physical Activity on Cortisol and Sleep: A Systematic Review and Meta-Analysis

De Nys L, Anderson K, Ofosu EF, Ryde GC, Connelly J, Whittaker AC. The effects of physical activity on cortisol and sleep: A systematic review and meta-analysis. *Psychoneuroendocrinology*. 2022;143:105843. doi:10.1016/j.psyneuen.2022.105843

KEY TAKEAWAY: Participation in regular physical activity may lead to improved sleep and lower cortisol levels. Overall, there is only a small fund of knowledge regarding this concern, and the research has limited generalizability.

STUDY DESIGN: Meta-analysis of intervention studies, which consisted of 10 randomized controlled trials

LEVEL OF EVIDENCE: STEP 2 (downgraded for limited generalizability)

BRIEF BACKGROUND INFORMATION: Most patients suffering from stress and lack of adequate sleep are counseled to participate in some form of physical activity. There is currently a lack of research and a paucity of information on how sleep and physical activity are interrelated. The goal of this systematic review was to pool the available data to determine if there was a difference in how a physical activity regimen changes stress levels and sleep quality.

PATIENTS: Adults between 27-64

INTERVENTION: Physical activity program

CONTROL: No physical activity program

PRIMARY OUTCOME: Cortisol levels in blood, hair, saliva, or urine

Secondary Outcome: Sleep quality measured using subjective data such as questionnaires, and objective data such as polysomnography, actigraphy, and accelerometry

METHODS (BRIEF DESCRIPTION):

- Researchers identified 3,412 unique studies and narrowed down 10 randomized control studies most relevant to answering their proposed clinical question using a three-researcher verification system.
- Regardless of health concerns, 756 adults aged 27–64 were selected from various countries (US, Jordan, UK, China, Switzerland).
- Physical activity programs (aerobic, weight-bearing activity) or movement-based mind-body approaches (yoga, Qigong) of any duration (2–5 times per week for 20–90 min per day or a total of 120–150 min per week for 3–16 weeks) were used as interventions.
- Patients receiving no interventions or other comparison interventions, including stretching, mindfulness, brain wave stimulation, home exercises, no exercise, and usual care, were used as comparisons.
- In the RCTs studied, outcomes were measured using either cortisol levels in blood, hair, saliva, or urine as a biological marker for stress.
    - Sleep quality was measured using subjective data, such as patient-reported questionnaires, and objective data, such as polysomnography, actigraphy, and accelerometry.
- The risk of bias was analyzed using the Cochrane Risk of Bias 2.0 tool and represented using Robvis software.
- Data of interest were analyzed utilizing the Chi-squared statistical test and comparing the groups on forest plots.

INTERVENTION (# IN THE GROUP): Number of studies by specific interventions (Aerobic: n=4, Mind-body: n=5, Dance: n=1, Extra breathing component: n=2)

COMPARISON (# IN THE GROUP): Number of studies by specific comparisons (Active control: n=3, no exercise: n=4, Usual care: n=2, Brain wave training or mindfulness: n=1)

FOLLOW-UP PERIOD: 3–16 weeks

RESULTS:

Primary Outcome –

- Regular exercise (aerobic, mind-body exercises, dance) showed statistically significant improvement in subjective measures of sleep measured by PSQI questionnaire compared to the control group (no exercise, brain-wave training/mindfulness).
    - Statistical mean difference in PSQI score between all studies (–0.30; 95% CI, –0.56 to –0.040].

- Physical exercise was associated with reduced levels of cortisol effect of regular exercise on cortisol levels.
    - Pooled data showed that exercise regimens led to statistically significant lower cortisol levels when compared to the comparison group.
    - Statistical mean difference in cortisol levels between all studies (–0.37; 95% CI, –0.52 to –0.21).

LIMITATIONS:

- Generalizability was limited as only 10% of patients were male.
- Six of the 10 studies included only females with breast cancer, limiting the ability to apply to the general population.
- The studies were sub-grouped by relevant control groups (active control, usual care, or waiting list) for both cortisol and sleep outcomes.
    - Additionally, six of the studies did not have a control group, which could increase the possibility of bias in the study overall.

Jared S. Machado, DO
Tripler Army Medical Center FMR
Honolulu, HI

Can Mindfulness Meditation Help with Anxiety and Depression in Patients with Insomnia?

A Mindfulness Meditation Mobile App Improves Depression and Anxiety in Adults with Sleep Disturbance: Analysis from a Randomized Controlled Trial

Huberty J, Puzia ME, Green J, et al. A mindfulness meditation mobile app improves depression and anxiety in adults with sleep disturbance: Analysis from a randomized controlled trial. *Gen Hosp Psychiatry*. 2021;73:30-37. doi:10.1016/j.genhosppsych.2021.09.004

KEY TAKEAWAY: Using a mindfulness meditation mobile application (app) significantly reduces anxiety and depression symptoms for patients with insomnia. Improvement in somatic and cognitive pre-sleep arousal increases the effectiveness of the mindfulness mediation app on reductions in depression and anxiety.

STUDY DESIGN: Non-blinded randomized control trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to non-blinded and selection bias)

BRIEF BACKGROUND INFORMATION: Anxiety and depression are among the leading causes of negative effects on health and well-being, including sleep disturbances (e.g., insomnia). Although there are several pharmacological (SSRIs, SNRIs, etc.) and non-pharmacological (e.g., cognitive behavioral therapy) treatments, a limited number of patients have access to the treatments because of cost and accessibility. Mindfulness meditation delivered via an app may be a way to reduce insomnia among patients with anxiety and depression.

PATIENTS: Adults with insomnia

INTERVENTION: A mindfulness meditation app

CONTROL: Waitlist

PRIMARY OUTCOME: Anxiety and depression symptoms

Secondary Outcome: Mediating roles of fatigue, daytime sleepiness, and pre-sleep arousal on the effect of the mindfulness app on anxiety and depression

METHODS (BRIEF DESCRIPTION):

- The study participants included patients with a mean age of 44 years old, with 78% female and 56% White.
- Inclusion criteria:
  - At least 18 years old
  - Read and understand English
  - Insomnia severity index score ≥10 with a range of 0–28, with higher scores indicative of worse insomnia
  - Inexperienced meditators (<1 hour/month)
- Participants were randomized into either an intervention group or a waitlist control group.
- Intervention: Participants used the "Calm" meditation app for at least 10 minutes daily but could also use it at their discretion.
- Participants filled out symptom scales at pre- and post-intervention.
  - Hospital anxiety and depression scale (HADS), ranging from 0–21, with higher scores indicating more severe anxiety and depression symptoms.
    - Minimal clinically important difference is 1.5 points.
  - Fatigue severity scale (FSS), ranging from 7–49, with higher scores indicating more severe fatigue.
  - The Epworth sleepiness scale (ESS), ranging from 0–24, with higher scores indicating more daytime sleepiness.
  - Pre-sleep arousal scale (PSA), ranging from 8–40, with higher scores indicating greater pre-sleep arousal.

INTERVENTION (# IN THE GROUP): 113

COMPARISON (# IN THE GROUP): 126

FOLLOW-UP PERIOD: Eight Weeks

RESULTS:

Primary Outcome –

- Compared to the control group, the intervention group significantly decreased depression and anxiety symptoms.
  - Depression symptoms (mean change: intervention, –1.3 vs control, 0.20; *P*<.001).
  - Anxiety symptoms (mean change: intervention, –1.8 vs control, 0.10; *P*<.001).

Secondary Outcome –

- Changes in somatic and cognitive PSA at mid-intervention fully mediated the effect of the mindfulness app on depression.
  - Somatic PSA (indirect effect = –0.47; 95% CI -0.90 to –0.13)

    - Cognitive PSA (indirect effect = –0.37; 95% CI –0.72 to –0.12)
- Changes in somatic and cognitive PSA at mid-intervention partially mediated the effect of the mindfulness app on anxiety.
    - Somatic PSA (indirect effect = –0.47; 95% CI –0.90 to –0.13)
    - Cognitive PSA (indirect effect = –0.40; 95% CI –0.73 to –0.14)

LIMITATIONS:

- Limited generalizability: Participants were mostly women who were more likely to use apps than men.
- Self-reported depression was significantly higher in the intervention group compared to the control group (*P*<.01).
    - Therefore, the improvements in symptoms might have been due to natural changes rather than actual, meaningful changes.

Jacob Stewart, MD
Saint Louis University Southwest Illinois FMR
O'Fallon, IL

Does Metformin Exposure In-Utero Lead to Increased BMI in Infants?

Outcomes in Children of Women with Type 2 Diabetes Exposed to Metformin Versus Placebo During Pregnancy (MiTy Kids): A 24-month Follow-up of the MiTy Randomised Controlled Trial

Feig DS, Sanchez JJ, Murphy KE, et al. Outcomes in children of women with type 2 diabetes exposed to metformin versus placebo during pregnancy (MiTy Kids): a 24-month follow-up of the MiTy randomised controlled trial. *Lancet Diabetes Endocrinol*. 2023;11(3):191-202. doi:10.1016/S2213-8587(23)00004-9

KEY TAKEAWAY: Exposure to metformin in-utero is not associated with a significant change in BMI at two years old.

STUDY DESIGN: Longitudinal follow-up of an RCT

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The incidence of pregnant women with type 2 diabetes is growing. Combined with the incidence of women diagnosed with gestational diabetes, the need for additional pharmacological agents has increased. Metformin is a relatively safe and well-tolerated diabetic medicine commonly used in gestational diabetes, but more research is needed on adverse outcomes such as infant adiposity.

PATIENTS: Infants born to type 2 diabetic mothers

INTERVENTION: Metformin exposure in utero

CONTROL: Placebo

PRIMARY OUTCOME: Change in BMI Z scores at two years old and mean sum of skinfolds

METHODS (BRIEF DESCRIPTION):

- Children from the MiTy Trial, a randomized controlled trial in which pregnant women with DM 2 were randomized to metformin or placebo, were invited to participate in this longitudinal cohort.
- Anthropometric measurements, such as weight, height, and skinfold thicknesses, were measured at 3,6,12 and 24 months old.
- Other demographic information like race, ethnicity, family medical history, family arrangement, and neonatal baseline information was noted.
- BMI was calculated, and z-scores were compared to WHO growth charts.
- The investigators used linear regression to compare the groups and adjusted for confounders, such as the patient's age at the time of measurement, infant sex, maternal BMI, and several other factors.

INTERVENTION (# IN THE GROUP): 111

COMPARISON (# IN THE GROUP): 115

FOLLOW-UP PERIOD: 2 years old

RESULTS:

Primary Outcome –

- There was no statistically significant difference between the mean BMI z-score of those exposed to metformin compared to placebo.
  - (MD 0.07 (95% CI, –0.31 to 0.45)
- The difference in mean skin fold was also not statically significant.
  - (MD 0.8 mm; 95% CI, –0.70 to 2.3)

LIMITATIONS:

- The study was not representative of the population that most often has type 2 DM in pregnancy and is therefore not generalizable.
  - Patients included in the study were mainly of European origin and not of low socioeconomic status.

Austin Gold MD
LewisGale Medical Center FMR
Roanoke, VA