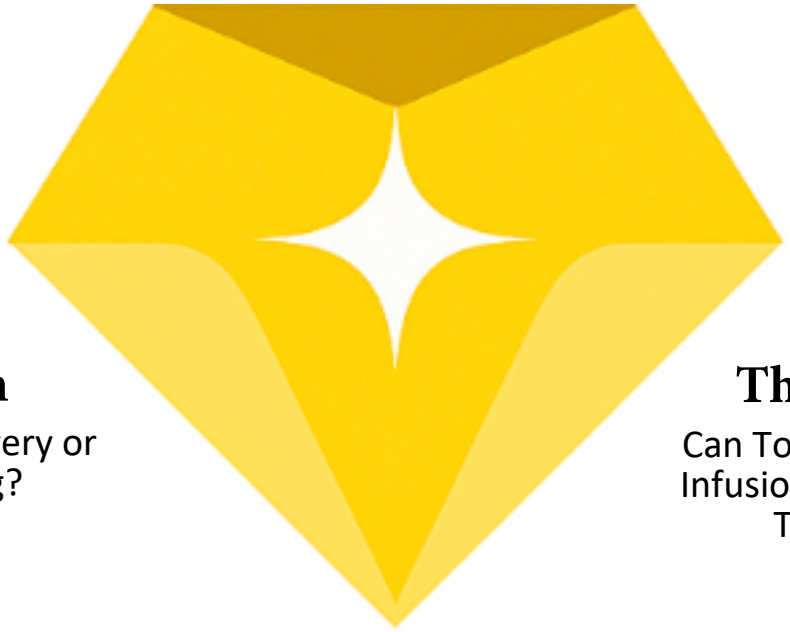
GOOD EVIDENCE MATTERS

GEMs of the Week



Mental Health

BPD in Teens: Recovery or Just Rebranding?

Thrombophlebitis

Can Topical Therapies Prevent Infusion Associated Superficial Thrombophlebitis?

SPOTLIGHT: Pregnancy

Double the Dose, Double the Success: Mifepristone Boosts Outcomes

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FPIN
Family Physicians Inquiries Network

Volume 5 Issue 34

Double the Dose, Double the Success: Mifepristone Boosts Outcomes in Early Pregnancy Loss

Treatment of Early Pregnancy Loss with Mifepristone and Misoprostol Compared with Misoprostol Only

Ci Friedman M, Mor L, Shazar R, et al. Treatment of Early Pregnancy Loss With Mifepristone and Misoprostol Compared With Misoprostol Only. *Obstet Gynecol*. 2025;145(2):204-209.
doi:10.1097/AOG.0000000000005800tation

KEY TAKEAWAY: Mifepristone combined with misoprostol lowers the likelihood of treatment failure in patients experiencing early pregnancy loss compared to misoprostol alone.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Early pregnancy loss affects up to 15% of clinically diagnosed pregnancies and often requires medical or surgical intervention to prevent complications. Misoprostol has traditionally been used as a monotherapy, but its success rate of about 75% leaves many patients needing further treatment. Recent studies suggest that combining mifepristone with misoprostol may improve outcomes, though long-term data on treatment failure remains limited. This study aimed to evaluate the long-term failure rate in early pregnancy loss between mifepristone, misoprostol dual therapy, and misoprostol treatment alone.

PATIENTS: Patients with early pregnancy loss

INTERVENTION: Mifepristone + misoprostol

CONTROL: Misoprostol alone

PRIMARY OUTCOME: Treatment failure

METHODS (BRIEF DESCRIPTION):

- Patients diagnosed with early pregnancy loss (anembryonic gestation or embryonic death) with gestational age ≤12 weeks by transvaginal ultrasound and treated at a single tertiary medical center from 2016–2023 were included in the study.
- Baseline demographics were similar between groups, though the mifepristone + misoprostol group had a slightly higher rate of smoking (13% vs 6.7%).
- The mifepristone + misoprostol group (May 2022–2023) received a single 200 mg oral dose of mifepristone 48 hours before 800 mcg of vaginal misoprostol. A second dose of misoprostol was offered at follow-up if needed.
- The misoprostol-only group (April 2016–2022) received 800 mcg (4 tablets of 200 mcg) of vaginal misoprostol initially; a second identical dose was administered at one-week follow-up if needed.
- Surgical intervention (elective or emergency dilation and curettage [D&C], or hysteroscopy) was offered based on follow-up ultrasound findings (e.g, uterine contents >15 mm) or clinical urgency.
- The primary outcome assessed treatment failure defined as the need for any surgical intervention (elective or emergency D&C or operative hysteroscopy) due to retained products of conception.
- Follow-up ultrasound was performed one-week post-treatment and again after menstruation to confirm complete evacuation or identify retained products.

INTERVENTION (# IN THE GROUP): 224

COMPARISON (# IN THE GROUP): 775

FOLLOW-UP PERIOD: Until patient's next menstruation and continued monitoring for late complications

RESULTS:

Primary Outcome –

- Mifepristone + misoprostol decreased the failure risk compared to misoprostol alone (18% vs 25%, respectively; relative risk [RR] 0.91, 95% CI, 0.84–0.97).
- Mifepristone + misoprostol improved gestational sac expulsion after the first course compared to misoprostol alone (71% vs 56%, respectively; RR 1.5; 95% CI, 1.2–1.9).
- Mifepristone + misoprostol did not significantly decrease the risk of switching to elective D&C compared to misoprostol alone (9.3% vs 14%, respectively; RR 0.95; 95% CI, 0.90–1.0).
- Mifepristone + misoprostol did not significantly decrease the risk of emergency D&C compared to misoprostol alone (5.3% vs 8.1%; RR 0.97; 95% CI, 0.93–1.0).
- Mifepristone + misoprostol did not significantly decrease the risk of operative hysteroscopy

compared to misoprostol alone (3.1% vs 3.3%, respectively; RR 0.99; 95% CI, 0.97–1.02).

LIMITATIONS:

- The study used a retrospective design, which may introduce selection and information bias.
- The number of patients in each group was unequal because the dual therapy protocol was implemented more recently, potentially affecting the comparison.
- Some patients may have received follow-up care or surgical treatment at other institutions, leading to incomplete outcome data.
- The study defined treatment success using a 15 mm endometrial thickness threshold, which is debated in literature and may overestimate failure rates.
- Loss to follow-up could have impacted the accuracy of long-term outcome assessment.

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BPD in Teens: Recovery or Just Rebranding?

Symptom Shifting From Nonsuicidal Self-Injury to Substance Use and Borderline Personality Pathology.
Steinhoff A, Cavelti M, Koenig J, Reichl C, Kaess M. Symptom Shifting From Nonsuicidal Self-Injury to Substance Use and Borderline Personality Pathology. *JAMA Netw Open*. 2024;7(11):e2444192. Published 2024 Nov 4. doi:10.1001/jamanetworkopen.2024.44192

KEY TAKEAWAY: Increased substance use may replace non-suicidal self-injury (NSSI) behaviors in adolescents with persistent borderline personality disorder (BPD).
STUDY DESIGN: Prospective longitudinal cohort
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: BPD typically develops in mid to late adolescence, with NSSI as a common manifestation. Previous studies have used changes in self-harm behavior, including NSSI, as a primary marker for treatment success. This study aimed to determine if a reduction in NSSI led to symptom shifting toward other risky behaviors, such as substance use, after BPD treatment.

PATIENTS: Adolescents with possible BPD
INTERVENTION: Behavioral therapy and psychiatric management
CONTROL: No control
PRIMARY OUTCOME: Changes in NSSI and substance use frequency and/or shifting from NSSI behavior to substance use
Secondary Outcome: Diagnosis of BPD, association with NSSI and substance use

METHODS (BRIEF DESCRIPTION):

- Participants being treated at a specialized outpatient clinic for BPD in Heidelberg, Germany were recruited for this prospective cohort study.
- Participants were included if they were 12–19 years old, with history of at least five NSSI incidents during the year prior to enrollment.
- Participant were an average age of 15 years old with 90% of participants being female.
- All participants received individualized behavioral health interventions based on symptom severity and treatment response.
- Treatment included cognitive behavioral therapy, dialectical behavioral therapy (group + individual), psychiatric management, and specialist crisis involvement.
- NSSI incidents were self-reported using the German version of the self-injurious thoughts and behaviors interview (SITBI).
- Substance use was self-reported using a questionnaire similar to the Youth Risk Behavior Survey (YBRS) where a score of 14 indicated daily alcohol and substance use.
- Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-4) criteria was used to assess BPD.
- Data was collected at baseline, one year, and two years after treatment.
- Participants were separated further into three groups based on the trajectory of their NSSI behavior and substance use.
    - Class one (32 participants): Joint decline of NSSI behavior and substance use.
    - Class two (210 participants): Decline of NSSI behavior with moderate increase of substance use.
    - Class three (34 participants): Decline of NSSI behavior with sharp increase of substance use
- Differences in BPD diagnoses were compared among the three groups at baseline and at two years.
- Cohen d was used to quantify the difference between a participant's baseline and follow up SITBI and YBRS scores.
    - Intercepts (baseline scores) and slopes (changes in scores) were used to estimate each participant's regression pathway.

INTERVENTION (# IN THE GROUP): 277
COMPARISON (# IN THE GROUP): Not applicable
FOLLOW-UP PERIOD: Two years

RESULTS:
Primary Outcome –

- Participants who completed at least one follow up had less substance use compared to participants who did not complete a follow up assessment (Cohen d –0.34; 95% CI, –0.58 to –0.10).

- Participants who completed at least one follow up had more NSSI behavior compared to participants who did not complete a follow up assessment (Cohen d 0.30; 95% CI, 0.07–0.54).
- After two years, NSSI behavior declined compared to baseline (mean latent intercept 3.6, *P*<.001; linear slope –0.95, *P*<.001).
- After two years, substance use increased compared to baseline (mean latent intercept 4.2, *P*<.001; linear slope 0.27, *P*=.02).

Secondary Outcome –

- Baseline BPD diagnosis was higher in class one compared to class two (mean standard error [SE] 4.6 vs 3.18; *P*=.001).
- Baseline BPD diagnosis was higher in class two compared to class three (mean SE 3.2 vs 4.29; *P*=.01).
- There was no significant difference in baseline BPD diagnosis between class one and class three.
- After two years, BPD diagnosis declined in class one compared to class three (mean SE 2.1 vs 5.2; *P*=.003)
- After two years, BPD diagnoses declined in class two vs class three (mean SE 2.5 vs 5.2; *P*=.004).
- After two years, there was no significant difference in BPD diagnosis between class one and class two.

LIMITATIONS:

- NSSI behavior and substance use were self-reported potentially underestimating a participant's true usage.
- There was a high rate of drop-out from the first to second follow-up.
- Generalizability is limited because participants had early access to treatment, which is not accessible in most countries. Also, the population studied was predominantly female.
- Follow up assessments were not completed at exactly one and two-year intervals and varied by a several months, which may affect results.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Navy, Defense Health Agency, Department of Defense, or the U.S. Government.

Can Topical Therapies Prevent Infusion Associated Superficial Thrombophlebitis?

Efficacy and Safety of Quick Penetrating Solution Heparin, Quick Penetrating Solution Diclofenac, and Heparin Gel in the Prevention of Infusion- Associated Superficial Thrombophlebitis: A Randomized Controlled Trial

Bajpai V, Patel TK, Dwivedi P, et al. Efficacy and safety of quick penetrating solution heparin, quick penetrating solution diclofenac, and heparin gel in the prevention of infusion-associated superficial thrombophlebitis: A randomized controlled trial. *Perspect Clin Res*. 2024;15(4):195-201. doi:10.4103/picr.picr_305_23

KEY TAKEAWAY: Prophylactic use of topical heparin preparations or diclofenac gel all have similar rates of superficial thrombophlebitis compared to one another.

STUDY DESIGN: Single-site, parallel, three-arm, randomized, open-labeled controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: Hospitalized patients frequently require intravenous (IV) cannulation for fluid and drug administration. Superficial thrombophlebitis (ST) can occur in up to 70% of patients requiring IV therapies, and this complication can be associated with deep vein thrombosis (DVT). Previous studies have shown some effectiveness in topical or IV heparin for treatment of ST, but more knowledge is needed about prevention strategies. This study compared the safety, efficacy and cost-effectiveness of three topical therapies in the prevention of ST which included quick penetrating solution (QPS) heparin, heparin gel and QPS diclofenac.

PATIENTS: Adult patients requiring IV cannulation

INTERVENTION: Topical QPS heparin, heparin gel, QPS diclofenac

CONTROL: Three-arm comparison

PRIMARY OUTCOME: Development of ST at 72 hours

Secondary Outcome: Mean time to ST

METHODS (BRIEF DESCRIPTION):

- This was an open-label, three-arm, parallel, randomized controlled study conducted at one site in India which included adults age 18–60 years old admitted for surgical intervention who required IV cannulation for at least 72 hours.
- Additional inclusion criteria were those in American Society of Anesthesiology (ASA) classes I or II, indicating healthy patients or with only mild, well controlled, systemic diseases.
- Those receiving IV irritants or preexisting phlebitis at another IV site, coagulation disorders, or hypersensitivity to the intervention medications were excluded.
- Participants had a mean age of 36 years, 50% were men, and there was no difference in terms of BMI or ASA class among the treatment groups.
- Eligible participants were randomized in a 1:1:1 ratio to one of 3 treatment arms: QPS heparin, heparin gel, and QPS diclofenac.
- The IV site was cleaned and the IV inserted under aseptic precautions and then the appropriate dose of the randomized drug was applied topically to the site and covered with waterproof dressing.
- Trained nursing staff not aware of the treatment groups assessed patients for ST development at eight, 16, 24, 32, 40, 48, 56, 64 and 72 hours using the Visual Infusion Phlebitis Scale.
    - This scale grades appearance of the IV site from 0–V, with a score of 0 indicating healthy skin and a score of V indicating advanced stage thrombophlebitis with induration and palpable venous cord.

INTERVENTION (# IN THE GROUP):

- Topical QPS heparin: 73
- Heparin gel: 73
- QPS diclofenac: 73

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: 72 hours

RESULTS:

Primary Outcome –

- There was no difference for the development of Grade ≥1 ST between heparin gel, QPS heparin, and QPS diclofenac (89% vs 91% vs 97%, respectively; *P*=.62).

Secondary Outcome –

- There was no difference in the mean time to Grade ≥1 or Grade ≥2 ST between heparin gel, QPS heparin, and QPS diclofenac.

LIMITATIONS:

- The study was open label without blinding, potentially introducing bias.
- The population was limited to very healthy (ASA I) surgical patients at one site in India, potentially limiting generalizability to other populations.
- The individual therapies were not compared to placebo therapy.

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NSAIDs and Oligohydramnios: A Fluid Situation

Use of Non-Steroidal Anti-Inflammatory Drugs in Pregnancy and Oligohydramnios: A Review

D'Ambrosio V, Vena F, Scopelliti A, et al. Use of non-steroidal anti-inflammatory drugs in pregnancy and oligohydramnios: a review. *J Matern Fetal Neonatal Med*. 2023;36(2):2253956. doi:10.1080/14767058.2023.2253956

KEY TAKEAWAY: Non-steroidal anti-inflammatory drug (NSAID) administration may increase the risk of reversible oligohydramnios compared to NSAID avoidance in patients at 17–35 weeks gestation with singleton pregnancies.

STUDY DESIGN: Systematic review of 11 case reports, four prospective trials, two retrospective studies, nine reviews, one case-control study, one randomized controlled trial, and one short communication (N=415).

LEVEL OF EVIDENCE: STEP 3 (downgraded due to inconsistency between studies, small sample sizes, and lack of statistical analysis)

BRIEF BACKGROUND INFORMATION: NSAIDs are considered first-line treatments for several conditions which affect pregnant patients. However, limited data regarding NSAID use in the second and third trimesters has associated NSAID use in a later pregnancy with oligohydramnios and resultant adverse fetal effects to include renal injury. This review aimed to assess the association between NSAID use after the 20th week of pregnancy and the development of oligohydramnios.

PATIENTS: Patients at 17–35 weeks gestation with singleton pregnancies

INTERVENTION: NSAID administration

CONTROL: Pregnant patients who were not treated with NSAIDs

PRIMARY OUTCOME: Development of oligohydramnios
Secondary Outcome: Time to resolution of oligohydramnios after cessation of NSAID use

METHODS (BRIEF DESCRIPTION):

- Existing literature was identified through searches in PubMed, Medline and Scopus databases for studies published from March 1988 to June 2022.
  - Studies were included if they had data on the relationship between oligohydramnios and NSAID use during pregnancy.
- Studies involving multiple pregnancies or animal species were excluded, as were studies unrelated to the authors' focus based on manual screening of abstracts.
- Patient median age was 20–36 years old. Patient median gestational age was 20–35 weeks.
- A total of 29 studies examining the effects of four NSAIDs on the development of oligohydramnios were reviewed.
  - 11 studies involving indomethacin examined doses ranging from 50 mg to 200 mg, and the frequency of dosing ranged from every six hours to once daily for a duration of 4–72 days; one of these also included ibuprofen 600–800 mg daily for the same duration of treatment.
  - Two studies involving diclofenac examined doses of 50 mg to 300 mg for 19–20 days.
  - Four studies involving nimesulide examined doses of 100 mg daily and 200 mg daily for a duration ranging from 3–52 days.
- Usual care was defined as the avoidance of NSAIDs after 20 weeks of pregnancy.
- Oligohydramnios was defined as either deepest vertical pocket <2 cm or amniotic fluid index <5 cm.
- Time to resolution of oligohydramnios after cessation of NSAID use was measured in terms of number of days.

INTERVENTION (# IN THE GROUP): 415

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- The use of indomethacin was associated with a rate of oligohydramnios between 5.7% and 70%, depending on the study (no statistical analysis completed).
- The use of ibuprofen was associated with a rate of oligohydramnios of 27% (no statistical analysis completed).
- The use of nimesulide was associated with a rate of oligohydramnios between 54–100% depending on the study (no statistical analysis completed).
- The use of diclofenac was associated with the development of oligohydramnios in two case reports.

Secondary Outcome –

- Reversibility of oligohydramnios was demonstrated in 11 of the 12 included studies for which this outcome was specified; time to restore amniotic fluid following treatment interruption was 1–10 days.

LIMITATIONS:

- There is considerable variation among included studies with respect to study design, sample size, and NSAID exposure (medication, dose, and treatment duration).
- The authors did not include statistical analysis data for the included controlled trials and cohort studies.
- While the authors report that 29 studies were included in the analysis, study characteristics were specified for only 18 of these.
- The study did not include a comprehensive statistical analysis.
- The study did not include an analysis of included study quality.

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Transcatheter Aortic-Valve Replacement: Let's Start to Help Asymptomatic Patients

Transcatheter Aortic-Valve Replacement for Asymptomatic Severe Aortic Stenosis

Généreux P, Schwartz A, Oldemeyer JB, et al. Transcatheter Aortic-Valve Replacement for Asymptomatic Severe Aortic Stenosis. *N Engl J Med*. 2025;392(3):217-227. doi:10.1056/NEJMoa2405880

KEY TAKEAWAY: Referral for transcatheter aortic valve replacement (TAVR) among patients with severe and asymptomatic aortic stenosis (AS) reduces the composite risk of death, stroke, or unplanned cardiovascular (CV) related hospitalization.

STUDY DESIGN: Prospective, multi-center, randomized, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Asymptomatic AS is one of the most diagnosed valvular diseases among those >65 years old. Current guidelines recommend valve replacement for patients with symptoms, or for those who are asymptomatic with any of the following: Left ventricular ejection fraction (LVEF) <50%; a stress test that is positive; another reason to have open-heart surgery. Asymptomatic patients without any of these complicating factors are recommended surveillance. The EARLY TAVR trial looked to see if there were improved outcomes with TAVR in patients with severe AS who were asymptomatic and without another indication for valve replacement.

PATIENTS: Adults with severe asymptomatic calcific AS

INTERVENTION: Early TAVR

CONTROL: Clinical surveillance (usual care)

PRIMARY OUTCOME: Composite of death, stroke, and CV-related hospitalizations

Secondary Outcome: Favorable health, left-sided heart health, change in LVEF, new atrial fibrillation (AF), death or disabling stroke

METHODS (BRIEF DESCRIPTION):

- Patients ≥65 years old with asymptomatic, severe calcific AS with suitable anatomy for repair and a LVEF >50% were included in the study.
  - Asymptomatic status was confirmed with stress test for 90.6 % of participants.
- The list of exclusionary criteria includes symptomatic AS, non-calcified or bicuspid aortic valve, and any pre-existing valve replacement, and others.
- Patients from 75 sites in the US and Canada were randomized 1:1 to either TAVR or clinical surveillance with standard care.
  - TAVR was completed using a SAPIEN 3 or SAPIEN 3 Ultra balloon-expandable valve.
  - Standard care included a yearly physical assessment, review of medications, electrocardiogram (EKG), transthoracic echocardiography (TTE), and a six-minute walk test, among others.
- Secondary outcomes were measured utilizing the following:
  - Kansas City Cardiomyopathy Questionnaire (KCCQ): Scores range from 0–100, with higher scores indicating fewer physical health limitations and overall greater feeling of wellness. Favorable health was defined as a score >75, not decreased >10 from baseline.
  - TTE: Evaluated left atrial (LA) volume index (≤34 mL/m^2), left ventricular (LV) longitudinal strain (≥15%), and LV mass index (<115 g/m^2 in men, and <95 g/m^2 in women) to assess for LA health, LV health, and LVEF.
  - Electrocardiogram results
  - History and physical assessment

INTERVENTION (# IN THE GROUP): 455

COMPARISON (# IN THE GROUP): 446

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- TAVR decreased the composite outcome of death, stroke, or unplanned CV hospitalization at two years compared to clinical surveillance (hazard ratio [HR] 0.50; 95% CI, 0.40–0.63).

Secondary Outcome –

- TAVR resulted in favorable health at two years compared to clinical surveillance (absolute risk difference [ARR] 19; 95% CI, 13–24).
- TAVR improved left-sided heart health at two years compared to clinical surveillance (ARR 12; 95% CI, 4.4–19).

- There was no statistically significant difference between groups regarding LVEF at two years, new onset AF, and death or disabling stroke.

LIMITATIONS:

- The committee was not blinded to assignment.
- The trial population was limited to predominantly White males, limiting generalizability.
- A difference between the surveillance included in the trial and real-world scenarios likely existed.

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