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Putting PCOS Complications INO Time-Out

Myo-inositol Supplementation to Prevent Pregnancy Complications in Polycystic Ovary Syndrome: A Randomized Clinical Trial

van der Wel AWT, Frank CMC, Bout-Rebel R, et al. Myo-inositol Supplementation to Prevent Pregnancy Complications in Polycystic Ovary Syndrome: A Randomized Clinical Trial. *JAMA*. 2025;334(13):1151-1159. doi:10.1001/jama.2025.13668

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KEY TAKEAWAY: Myo-inositol 4 g + folic acid 0.4 mg daily does not significantly reduce the composite of gestational diabetes, preeclampsia, or preterm birth <37 weeks compared to folic acid 0.4 mg daily in pregnant individuals with polycystic ovary syndrome (PCOS).

STUDY DESIGN: Multicenter, double-blind, randomized placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Individuals with PCOS are at increased risk for adverse pregnancy outcomes. Although smaller, non-blinded studies suggested that myo-inositol may improve insulin sensitivity and reduce these risks, high-quality randomized controlled trial evidence has been limited. This study aimed to determine whether myo-inositol supplementation during pregnancy reduces the risk of adverse pregnancy outcomes among individuals with PCOS.

PATIENTS: Pregnant individuals with a prior PCOS diagnosis and a singleton pregnancy

INTERVENTION: Myo-inositol 4 g + folic acid 0.4 mg daily

CONTROL: Placebo (0.4 mg folic acid only)

PRIMARY OUTCOME: Composite of gestational diabetes, preeclampsia, or preterm birth

Secondary Outcome: Maternal and neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- The study enrolled 464 pregnant individuals ≥18 years old with PCOS and a singleton pregnancy at 8–16 weeks' gestation.
- Paitents were adults with a mean age of 32 years and median pre-pregnancy BMI of 25.
- Most patients were white (86%), nulliparous (66%), and many of them were conceived via assisted reproduction (68%).
- Individuals with pre-existing diabetes, kidney failure, or hypoglycemic medication use were excluded.
- Patients were randomized to receive either Myo-inositol 2 g + folic acid 0.2 mg twice daily vs matching placebo containing folic acid 0.2 mg twice daily, from randomization until delivery.
- Adherence was monitored by sachet counts, with ≥80% of doses taken considered good adherence.
- Supplementation continued from randomization until delivery.
- The primary outcome measured the composite outcome of gestational diabetes, preeclampsia, or preterm birth before 37 weeks.
- Maternal outcomes included gestational hypertension, thromboembolism, pregnancy-related hospitalization, mode of delivery, shoulder dystocia, postpartum hemorrhage, obstetric anal sphincter injury, breastfeeding, treatment adherence, adverse effects, and HbA1c.
- Neonatal outcomes included gestational age at birth, birth weight, sex, small- or large-for-gestational-age status, neonatal intensive care unit (NICU) admission, time from randomization to birth, five-minute Apgar score <7, stillbirth, neonatal death, congenital anomalies, birth injury, and neonatal hypoglycemia requiring intravenous (IV) glucose.

INTERVENTION (# IN THE GROUP): 230

COMPARISON (# IN THE GROUP): 234

FOLLOW-UP PERIOD: Maternal and neonatal outcomes were assessed through birth, with additional follow-up at six weeks postpartum

RESULTS:

Primary Outcome –

- Myo-inositol 4 g + folic acid 0.4 mg daily did not reduce the composite of gestational diabetes, preeclampsia, or preterm birth <37 weeks compared to placebo (25% vs 27%, respectively; relative risk [RR] 0.93; 95% CI, 0.68–1.3).

Secondary Outcome –

- Myo-inositol 4 g + folic acid 0.2 mg daily reduced primary cesarean delivery compared to placebo (5.9% vs 12%, respectively; RR 0.51; 95% CI, 0.27–0.97).

- There was no significant difference in other maternal or neonatal outcomes for the intervention group compared to placebo.

LIMITATIONS:

- Medication adherence was suboptimal, as only 39% of patients in the intervention group achieved the predefined 80% adherence threshold.
- The study population was predominantly White (86%), which may limit generalizability to more diverse populations.
- Investigators did not collect detailed data on baseline diet or physical activity, limiting assessment of lifestyle-related confounding factors.
- Variability in prenatal care practices across providers may have resulted in inconsistent patient education and differences in pregnancy management.

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Closing the Cervical Cancer Screening Gap

Self-Collection for Cervical Cancer Screening in a Safety-Net Setting: The PRESTIS Randomized Clinical Trial

Montealegre JR, Hilsenbeck SG, Bulsara S, et al. Self-Collection for Cervical Cancer Screening in a Safety-Net Setting: The PRESTIS Randomized Clinical Trial. *JAMA Intern Med*. 2025;185(9):1119-1127. doi:10.1001/jamainternmed.2025.2971

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KEY TAKEAWAY: Self-collection is effective for increasing cervical cancer screening participation in an under-screened safety-net population.

STUDY DESIGN: Parallel, single-blinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to being single-blinded)

BRIEF BACKGROUND INFORMATION: Cervical cancer screening participation remains below the Healthy People 2030 target of 79%, particularly among underserved populations. This study evaluated whether mailed self-collection kits could increase cervical cancer screening participation in a safety-net health system.

PATIENTS: Individuals with a cervix, 30–65 years old, who were not up to date on cervical cancer screening

INTERVENTION: Telephone reminder + mailed cervical cancer screening self-collection kit; or telephone reminder + mailed self-collection kit with an additional patient navigation call

CONTROL: Telephone reminder only for clinic-based cervical cancer screening

PRIMARY OUTCOME: Cervical cancer screening participation within six months

Secondary Outcome: Positive high-risk HPV results, completion of recommended follow-up within six months

METHODS (BRIEF DESCRIPTION):

- Adults needing cervical cancer screening were recruited for a pragmatic, parallel, single-blinded randomized trial evaluating self-collection interventions compared with usual clinic-based screening reminders.
- Participants were 30–65 years old and received care in a publicly funded safety-net health system in Houston, Texas.
- Inclusion criteria included those who did not have a history of hysterectomy or cervical cancer diagnosis, had ≥2 ambulatory care visits in the past five years, and had no cytology in the past 3.5 years or no HPV testing in the past 5.5 years.
- Patients with no telephone contact information in the electronic health record, those lacking a primary care provider outside the health system, or documented history of cervical dysplasia in the past 3.5 years were excluded.
- The median age was 49 years (IQR, 39–57); 94% of participants were from racial or ethnic minoritized populations, and 56% were covered by the county's publicly funded financial assistance program.
- All participants received a telephone reminder from a patient navigator to attend clinic-based cervical cancer screening.
- The first intervention group also received a mailed Aptima HPV test (Hologic) and reflex testing for HPV16 and HPV 18/45.
- The self-collection + patient navigation group received the same mailed self-collection kit + an additional patient navigation telephone call.
- Kits were mailed and patients were given six months to return their samples.
- The comparison group received only a telephone reminder concerning telehealth and the need for cervical cancer screening in clinic.
- The primary outcome was cervical cancer screening participation within six months, defined as either attendance for clinic-based screening or return of a mailed self-collection kit.
- Secondary outcomes included screening modality, positive high-risk HPV results, and completion of recommended follow-up within six months.

INTERVENTION (# IN THE GROUP):

- TR+ mailed SC Kit: 828
- TR+ mailed SC kit + patient navigation: 818

COMPARISON (# IN THE GROUP):

- Telephone reminder only group: 828

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Telephone reminders + mailed self-collection increased cervical cancer screening participation

compared to telephone reminders alone (relative participation 2.4; 95% CI, 2.0–2.8).

- Telephone reminders + mailed self-collection and patient navigation increased cervical cancer screening participation compared to telephone reminders alone (relative participation 2.7; 95% CI, 2.3–3.2).

Secondary Outcome –

- Among participants who completed screening in either self-collection group, 84 of 609 (14%) had a positive high-risk HPV result.
- Among those who completed an in-clinic-based screening, nine of 256 participants screened in clinic (3.5%) had a positive HPV result requiring follow-up.
- Of the self-collection kit group, 61% completed follow-up within six months, and 69% in the self-collection kit group with patient navigation.
- Among those who completed an in-clinic-based screening, four of nine (44%) completed follow-up within six months.

LIMITATIONS:

- Participants were aware of the self-collection kit offering, which may have influenced participation.
- The study occurred during the COVID-19 pandemic, which may have inflated participation in self-collection.
- Patient navigators were not blinded.
- Self-collection kits were not FDA approved for home use until after completion of the trial.

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But Does It Save Lives? Colonoscopy for Colon Cancer Screening

Long-Term Effects of Colonoscopy Screening on Colorectal Cancer Incidence and Mortality: A Multicountry, Population-Based Randomized Controlled Trial

Kaminski MF, Kalager M, Løberg M, et al. Long-term effects of colonoscopy screening on colorectal cancer incidence and mortality: a multicountry, population-based randomized controlled trial. *Lancet*. 2026;407(10541):1787-1795. doi:10.1016/S0140-6736(26)00508-8

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KEY TAKEAWAY: Invitation to colon cancer screening by colonoscopy reduces the incidence of colon cancer by 19%, but does not prevent deaths from colon cancer.

STUDY DESIGN: Randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Colon cancer screening can take many forms, including a stool test, CT, flexible sigmoidoscopy, or colonoscopy. RCTs support both stool tests and flexible sigmoidoscopy, but this is the first RCT to compare colonoscopy with no screening. A 10-year follow-up to this study was published previously and found a decrease in colon cancer incidence but not colon cancer mortality. This study evaluated long-term effects on colon cancer incidence and mortality.

PATIENTS: Adults 55–64 years old with no prior colon cancer screening

INTERVENTION: Invitation for colon cancer screening by colonoscopy

CONTROL: No invitation

PRIMARY OUTCOME: Colon cancer incidence and mortality

Secondary Outcome: Colon cancer incidence and mortality by per-protocol analysis, all-cause mortality, and subgroup analyses by age, gender, and location

METHODS (BRIEF DESCRIPTION):

- Adults 55–64 years old with no prior history of colon cancer screening were recruited from Northern Europe.
- Patients were randomized to receive an invitation to colon cancer screening by colonoscopy or no invitation.
- Consenting patients underwent colonoscopy to screen for colon cancer.
- The intervention group received a letter inviting them to one screening colonoscopy; endoscopists removed feasible lesions and biopsied tumors.
- The comparison group was not screened for colorectal cancer.
- Investigators linked national cancer and cause-of-death registries to measure 13-year colorectal cancer incidence, colorectal cancer mortality, and all-cause mortality.
- All patients were followed for the primary outcomes of colon cancer mortality and incidence, which were identified through national cancer and cause-of-death registries.
- Secondary outcomes included colon cancer mortality and incidence by per-protocol analysis, all-cause mortality, and subgroup analyses by age, gender, and location.

INTERVENTION (# IN THE GROUP): 28,217

COMPARISON (# IN THE GROUP): 56,366

FOLLOW-UP PERIOD: 13 years

RESULTS:

Primary Outcome –

- Invitation to colon cancer screening decreased colon cancer incidence compared to control (relative risk [RR] 0.81; 95% CI, 0.71–0.90; NNI=294).
- Invitation to colon cancer screening did not reduce colon cancer mortality compared to control (RR 0.88; 95% CI, 0.68–1.1).

Secondary Outcome –

- Invitation to colon cancer screening decreased colon cancer incidence by per-protocol analysis (RR 0.55; 95% CI, 0.33–0.81; NNI=125), but not colon cancer or all-cause mortality.
- Invitation to colon cancer screening in men decreased colon cancer incidence compared to control (RR 0.77; 95% CI, 0.64–0.88; NNI=200), but not mortality.
- Invitation to colon cancer screening in women did not improve colon cancer incidence or mortality.
- Invitation to colon cancer screening in adults 55–59 years old did not improve colon cancer incidence or mortality.

- Invitation to colon cancer screening in adults 60–64 years old decreased colon cancer incidence compared to control (RR 0.75; 95% CI, 0.62–0.85; NNI=175), but not mortality.
- Invitation to colon cancer screening did not improve proximal colon cancer incidence or mortality.
- Invitation to colon cancer screening decreased distal colon cancer incidence compared to control (RR 0.79; 95% CI, 0.65–0.89; NNI=416), but not mortality.

LIMITATIONS:

- Only 42% of patients who were invited to colon cancer screening by colonoscopy underwent colonoscopy.
- Patients were not blinded to the intervention.
- Generalizability is limited due to the study only including Northern European countries.

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The End of Trial and Error? A Clinical Decision-Support Tool for Personalized Depression Treatment

A Decision-Support System to Personalize Antidepressant Treatment in Major Depressive Disorder: A Randomized Clinical Trial

Cipriani A, Fernandes KBP, Mulsant BH, et al. A Decision-Support System to Personalize Antidepressant Treatment in Major Depressive Disorder: A Randomized Clinical Trial. *JAMA*. 2026;335(14):1219-1231. doi:10.1001/jama.2026.1327

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KEY TAKEAWAY: In adults with major depressive disorder (MDD), a web-based clinical decision-support tool to personalize treatment increases the likelihood of continuing treatment through eight weeks by 10% while also improving depressive and anxiety symptoms at 24 weeks.

STUDY DESIGN: Multicenter, non-blinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: MDDs are a leading cause of global health burden with over 280 million people affected. However, treatment success is influenced by the disorder's complex etiology and symptomatology. Clinicians struggle to predict the efficacy and tolerability of antidepressants, leading to frequent and early treatment discontinuation. This study attempted to reduce treatment discontinuation using a clinical decision-support tool to personalize treatment.

PATIENTS: Adults 18–74 years old with MDD

INTERVENTION: Use of a web-based clinical decision-support system to personalize antidepressant treatment

CONTROL: Usual care

PRIMARY OUTCOME: Treatment discontinuation due to any cause

Secondary Outcome: Adverse event-related discontinuation, depressive symptoms, anxiety symptoms

METHODS (BRIEF DESCRIPTION):

- The study was conducted at 47 sites in Brazil, Canada, and the UK.
- Adults 18–74 years old with MDD who had an indication for pharmacological treatment and were willing to take an antidepressant as monotherapy were included in the study.
- Exclusion criteria included treatment-resistant depression, medical conditions (including pregnancy, arrhythmia, or QT prolongation), or requiring urgent mental health care or hospital admission.
- Patients were randomized 1:1 to the Personalizing Antidepressant Treatment for Unipolar Depression Combining Individual Choices, Risks and Big Data (PETRUSHKA) tool or usual care.
- The PETRUSHKA tool was used to select an antidepressant for each participant.
  - Based on each participant's demographic and clinical characteristics, the tool predicted the performance of each drug for each outcome.
  - These predictions were combined with patient preferences about adverse events to create a list of the top three antidepressants.
  - These recommended antidepressants were used to inform the discussion and final treatment selection between clinician and patient.
- The primary outcome was treatment discontinuation due to any cause at eight weeks. Dose alterations were allowed, but medication changes were not.
- Secondary outcomes were the following:
  - Discontinuation due to adverse events at eight weeks.
  - Self-rated change in depressive and anxiety symptoms were measured at eight and 24 weeks.
  - Depressive symptoms were measured using a nine-item Patient Health Questionnaire (PHQ-9). Scores range from 0–27, with higher scores indicating more severe depression.
  - Anxiety symptoms were measured using the Generalized Anxiety Disorder seven-Item Questionnaire (GAD-7). Scores range from 0–21, with higher scores indicating more severe anxiety.

INTERVENTION (# IN THE GROUP): 241

COMPARISON (# IN THE GROUP): 252

FOLLOW-UP PERIOD:

- Primary outcome: Eight weeks
- Secondary outcomes: 24 weeks

RESULTS:

Primary Outcome –

- Antidepressant discontinuation due to any cause at eight weeks was lower in the PETRUSHKA group compared to usual care (17% vs 27%, respectively; adjusted relative risk [aRR] 0.62; 95% CI, 0.44–0.88; NNT=10).

Secondary Outcome –

- Antidepressant discontinuation due to adverse events at eight weeks was lower in the PETRUSHKA group compared to usual care (9% vs 16%, respectively; aRR 0.59; 95% CI, 0.36–0.97).
- At 24 weeks, the mean PHQ-9 score was lower in the PETRUSHKA group compared to usual care (7.1 vs 9.2, respectively; adjusted between-group mean difference −1.9; 95% CI, −3.1 to −0.78).
- At 24 weeks, the mean GAD-7 score was lower in the PETRUSHKA group compared to usual care (4.6 vs 5.8, respectively; adjusted between-group mean difference −1.4; 95% CI, −2.3 to −0.52).

LIMITATIONS:

- Patients and clinicians were not blinded.
- More than 80% of participants were White, limiting generalizability.
- The tool lacked complete data for certain antidepressants (e.g. reboxetine, sertraline).
- Missing secondary outcome data created a risk of attrition bias and uncertainty regarding long-term effects.

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Management of Psychiatric Symptoms with a Conversational AI Platform

Efficacy of a Conversational AI Agent for Psychiatric Symptoms and Digital Therapeutic Alliance: A Randomized Clinical Trial Shoshani A, Gurfinkel B, Kor A, et al. Efficacy of a Conversational AI Agent for Psychiatric Symptoms and Digital Therapeutic Alliance: A Randomized Clinical Trial. *JAMA Netw Open*. 2026;9(4):e266713. Published 2026 Apr 1. doi:10.1001/jamanetworkopen.2026.6713

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KEY TAKEAWAY: In Israeli university students experiencing mild to moderate psychological distress, a conversational artificial intelligence (AI) platform is modestly effective in reducing symptoms of anxiety and depression while improving well-being and life satisfaction.

STUDY DESIGN: Three-arm, parallel-group, randomized clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to three-month follow-up attrition rate of about 35%; blinding was not possible due to the "nature of the interventions")

BRIEF BACKGROUND INFORMATION: Structural constraints in traditional mental health care, such as provider shortages and stigma, have created a significant global treatment gap. Digital mental health interventions offer a scalable solution but often suffer from high user attrition due to nonrelational designs. This study evaluates whether a conversational AI platform can simulate a therapeutic alliance to improve mental health outcomes.

PATIENTS: University students (18–35 years old) in Israel reporting psychological distress

INTERVENTION: 12-week conversational AI platform (Kai)

CONTROL: Face-to-face group therapy or a waiting list control

PRIMARY OUTCOME: Anxiety, depression, posttraumatic stress disorder (PTSD), well-being, and life satisfaction

Secondary Outcome: Intention to seek therapy

METHODS (BRIEF DESCRIPTION):

- 995 Israeli university students were recruited through university networks and online platforms.
- Inclusion criteria included a score of ≥3 on the anxiety or depression subscales of the PHQ-4, Hebrew fluency, and internet access.
- Exclusion criteria included active suicidal ideation, current psychotherapy or psychiatric medication, and a history of severe mental disorders.
- The AI group had unrestricted access to Kai, a digital platform that delivered personalized treatment based on principles of cognitive behavioral therapy (CBT), acceptance and commitment therapy, dialectical behavior therapy (DBT), mindfulness, and positive psychology.
- The face-to-face group therapy cohort attended 12 weekly 90-minute sessions facilitated by licensed psychologists.
- The waiting list control received no active intervention but was offered access after the study.
- The primary outcome measured anxiety, depression, PTSD, well-being, and life satisfaction.
  - Anxiety was measured using the GAD-7. Scores range from 0–21, with higher scores indicating greater severity.
  - Depression was measured using the PHQ-9. Scores range from 0–27, with higher scores indicating greater severity.
  - PTSD was measured using the brief PTSD checklist for DSM-5. Scores range from 0–16, with higher scores indicating greater PTSD symptom severity.
  - Well-being was measured using the WHO-5-Well-Being-Index. Scores were converted to a 0–100 scale, with higher values indicating greater well-being.
  - Life satisfaction was measured using the Brief Multidimensional Students' Life Satisfaction Scale. Scores range from 5–35, with higher scores indicating greater life satisfaction.
- The secondary outcome, intention to seek therapy, was evaluated via two primary methods.
  - Using one item from the General Help-Seeking Questionnaire.
  - Asking patients a yes-or-no question specifically regarding their plans to start therapy within the next three months.

INTERVENTION (# IN THE GROUP): 336

COMPARISON (# IN THE GROUP):

- Group therapy: 331

- Wait list control: 328

FOLLOW-UP PERIOD: 12-week intervention with three-month follow-up

RESULTS:

Primary Outcome –

- AI reduced anxiety symptoms compared to group therapy and control.
  - Group therapy (mean difference [MD] –2.2; 95% CI, –2.7 to –1.7)
  - Control (MD –2.2; 95% CI, –2.7 to –1.7)
- AI reduced depression symptoms compared to group therapy and control.
  - Group therapy (MD –0.69; 95% CI, –1.3 to –0.04)
  - Control (MD –2.0; 95% CI, –2.6 to –1.4)
- AI did not significantly reduce PTSD symptoms compared to group therapy or control.
  - Group therapy (MD –0.29; 95% CI, –0.85 to 0.27)
  - Control (MD –0.49; 95% CI, –1.1 to 0.07)
- AI increased well-being scores compared to group therapy and control.
  - Group therapy (MD 5.7; 95% CI, 2.7–8.7)
  - Control (MD 9.2; 95% CI, 6.1–12)
- AI increased life satisfaction scores compared to group therapy and control.
  - Group therapy (MD 1.2; 95% CI, 0.23–2.1)
  - Control (MD 2.6; 95% CI, 1.6–3.5)

Secondary Outcome –

- Intention to seek therapy declined in the AI group (30% to 24%) but increased in the control group (34% to 37%).

LIMITATIONS:

- The outcomes were self-reported.
- The study experienced substantial attrition at the three-month follow-up.
- Long-term cost-effectiveness and functional recovery are unknown.
- The observed decline in therapy-seeking intention could possibly lead to unmet needs if individuals solely rely on AI without escalating to human care when necessary.

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