

GEMs of the Week



SPOTLIGHT

The Progesterone Proposition

A New Look at HDP Prevention

Kawasaki Conundrum

Is IVIG Enough Without Aspirin?

Peeling Back the Benefits

Daily Oranges Reduce Hepatic Steatosis in MASLD Patients

The Progesterone Proposition: A New Look at HDP Prevention

Vaginal Micronized Progesterone for the Prevention of Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-Analysis

Melo P, Devall A, Shennan AH, et al. Vaginal micronised progesterone for the prevention of hypertensive disorders of pregnancy: A systematic review and meta-analysis. *BJOG*. 2024;131(6):727-739. doi:10.1111/1471-0528.17705

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KEY TAKEAWAY: Vaginal micronized progesterone, when started in the first trimester, may reduce the risk of hypertensive disorders of pregnancy (HDP) and pre-eclampsia.

STUDY DESIGN: Systematic review and meta-analysis of 11 randomized controlled trials (RCTs) (N=9,924)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: HDP and pre-eclampsia are common pregnancy complications with potential adverse effects on mother and baby. Vaginal progesterone in high-risk pregnancies reduces the risk of miscarriage and preterm birth, but complications like HDP and pre-eclampsia have not been studied. This study explored if treatment with vaginal progesterone can reduce the risk of HDP and pre-eclampsia.

PATIENTS: Pregnant women

INTERVENTION: Vaginal micronized progesterone

CONTROL: Placebo

PRIMARY OUTCOME: HDP and pre-eclampsia rates

METHODS (BRIEF DESCRIPTION):

- RCTs from MEDLINE, Embase, PubMed, the Cochrane Central Register of Controlled Trials, and clinicaltrials.gov from inception with vaginal progesterone that were compared to placebo was included in the study.
- Pregnant women >15 with gestational age ranging 6–36 weeks with singleton or twins were included in the study.
- Non-pregnant participants, non-vaginal routes of progesterone, untrustworthy studies via Cochrane recommendations, or selection bias risk greater than low were excluded from the study.
- Two investigators independently performed final study selection, data extraction, and quality assessment via Cochrane Risk of Bias 2 tool.

- The intervention included vaginal micronized progesterone with total daily dose ranging between 100–800 mg.
- HDP is defined as after 20 weeks gestation, new onset, sustained, systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg with or without proteinuria.
- Pre-eclampsia is defined as HDP with additional systemic findings of proteinuria, kidney impairment, liver dysfunction, neurological features, hemolysis, thrombocytopenia, or fetal growth restriction.
- Data was analyzed with forest plots with random effects model (risk ratio, 95% CI, and $I^2 < 50\%$ low heterogeneity), sensitivity analyses, progesterone dose subgroup analysis, and GRADE.

INTERVENTION (# IN THE GROUP): 5,000

- First trimester: 2,622
- Second or third trimester: 2,378

COMPARISON (# IN THE GROUP): 4,924

- First trimester: 2,654
- Second or third trimester: 2,270

FOLLOW-UP PERIOD: Unavailable

RESULTS:

Primary Outcome –

- Vaginal micronized progesterone in the first trimester significantly reduced rates of HDP compared to placebo (2 studies, n=4,431; risk ratio [RR] 0.71; 95% CI, 0.53–0.93; $I^2=0\%$).
 - Vaginal micronized progesterone 400 mg BID dosing was the most effective at reducing HDP (1 study, n=4,153; RR 0.74; 95% CI, 0.55–0.99).
- Vaginal micronized progesterone in the first trimester significantly reduced pre-eclampsia compared to placebo (3 studies, n=562; RR 0.61; 95% CI, 0.41–0.92; $I^2=0\%$).
 - Vaginal micronized progesterone 400 mg BID dosing was the most effective at reducing pre-eclampsia (3 studies, n=526; RR 0.61; 95% CI, 0.41–0.92; $I^2=0\%$).
- Vaginal micronized progesterone in the second and third trimester showed no significant difference in reducing HDP compared to placebo (3 studies, n=1,602; RR 1.2; 95% CI, 0.67–2.1; $I^2=9\%$).

- Starting vaginal micronized progesterone in the second and third trimester showed no significant difference in reducing pre-eclampsia compared to placebo (5 studies, n=4,274; RR 0.97; 95% CI, 0.71–1.3; I²=0%).
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LIMITATIONS:

- RCTs focused on specific groups of women which included those at risk of preterm birth, threatened miscarriage, and multiple gestations.
 - RCTs primary outcomes mainly assessed miscarriage or preterm birth; this metaanalysis evaluated secondary outcomes, like HDP.
 - Confounding factors, including history of preterm birth, twin's vs singleton, age, body mass index [BMI], and use of aspirin, were not adjusted for.
 - Other modalities of progesterone administration were excluded.
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Intravenous Immunoglobulin Alone for Coronary Artery Lesion Treatment of Kawasaki Disease: A Randomized Clinical Trial

Kuo HC, Lin MC, Kao CC, et al. Intravenous Immunoglobulin Alone for Coronary Artery Lesion Treatment of Kawasaki Disease: A Randomized Clinical Trial. *JAMA Netw Open*. 2025;8(4):e253063. Published 2025 Apr 1. doi:10.1001/jamanetworkopen.2025.3063
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KEY TAKEAWAY: For children with Kawasaki disease (KD), intravenous immunoglobulin (IVIG) alone appears to be as good as IVIG + aspirin for preventing coronary artery lesions (CALs).

STUDY DESIGN: Multicenter, single blind, non-inferiority randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to single-blinded study, homogenous patient population, and lack of intention-to-treat analysis)

BRIEF BACKGROUND INFORMATION: KD is an acute vasculitis primarily affecting children <5 years old. The most worrisome complication of KD is CALs, such as aneurysms and infarctions. This study aimed to ascertain whether IVIG alone would affect the development of CALs compared to standard care with IVIG + aspirin in the acute phase of treatment.

PATIENTS: Children <6 years old with Kawasaki disease

INTERVENTION: IVIG alone

CONTROL: IVIG + aspirin

PRIMARY OUTCOME: Development of CALs at six weeks
Secondary Outcome: Development of CALs at six months, IVIG resistance

METHODS (BRIEF DESCRIPTION):

- Investigators recruited patients for this randomized, non-inferiority trial from seven medical centers in Taiwan.
- Participants <6 years old with a diagnosis of typical KD, defined as fever ($>38^{\circ}\text{C}$ ear temperature) ≥ 5 days, as well as four of the five following symptoms:
 - Diffuse mucosal inflammation (e.g. strawberry tongue, dry and cracked lips)
 - Bilateral non-purulent conjunctivitis
 - Dysmorphic skin rashes

- Indurative edematous change over the hands and feet or desquamation over the fingertips or toes
- Cervical lymphadenopathy (≥ 1 node at least 1.5 centimeter in diameter)
- Participants with fever outside of 5–10 days, atypical KD, or prior treatment with immunosuppressives were excluded from the study.
- Participants were 1.8 years old on average, most were male (61%), and the IVIG alone group had lower C-reactive protein levels compared to the IVIG plus aspirin group (42 mg/L vs 68 mg/L, respectively).
- Participants were randomized 1:1 to IVIG (2 g/kg) alone or IVIG (2 g/kg) + aspirin (80–100 mg/kg/day in four doses) with IVIG given over 10–12 hours.
 - All participants then received low-dose aspirin (3–5 mg/kg/day) after the initial treatment for at least six weeks.
- The primary outcome was measured by pediatric cardiologists using the luminal diameter of the left main, left anterior descending, and right coronary artery by echocardiogram at six weeks.
 - Abnormal coronary artery diameter was defined as:
 - >3 mm in those <5 years old
 - >4 mm in those ≥ 5 years
 - Internal diameter at least 1.5 times the diameter of an adjacent segment
 - Luminal irregularity with z-score >2.5 calculated with data from Taiwan Society of Pediatric Cardiology
- The non-inferiority margin for the primary outcome was set at 10%.
- The secondary outcomes were development of CALs at six months and IVIG resistance, defined as recurrent or persistent fever between 2–7 days after the first IVIG treatment.

INTERVENTION (# IN THE GROUP): 69

COMPARISON (# IN THE GROUP): 65

FOLLOW-UP PERIOD: 6 months

RESULTS:

Primary Outcome –

- IVIG + aspirin did not significantly affect the development of CALs at six weeks compared to IVIG alone, and it was below the non-inferiority margin (between-group difference 3.6%; 97.5% CI, -100 to 8.1).

Secondary Outcome –

- IVIG + aspirin did not significantly affect the development of CALs at six months and IVIG resistance compared to IVIG alone.

LIMITATIONS:

- Participants were East Asian in origin, limiting generalizability to other populations.
- Patients with atypical KD were not explicitly studied, further limiting generalizability.
- There were few patients with CALs in both groups, potentially limiting ability to detect a difference, should one exist.
- Because aspirin was administered after the acute phase of KD in both treatment arms, it is unknown if omitting prophylactic aspirin would affect CAL development.
- No intention-to-treat protocol performed.

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Peeling Back the Benefits: Daily Oranges Reduce Hepatic Steatosis in MASLD Patients

Daily Orange Consumption Reduces Hepatic Steatosis Prevalence in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease: Exploratory Outcomes of a Randomized Clinical Trial

Notarnicola M, Tutino V, De Nunzio V, et al. Daily Orange Consumption Reduces Hepatic Steatosis Prevalence in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease: Exploratory Outcomes of a Randomized Clinical Trial. *Nutrients*. 2024;16(18):3191. Published 2024 Sep 20. doi:10.3390/nu16183191

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KEY TAKEAWAY: Daily orange consumption for four weeks reduces liver steatosis in adults with metabolic dysfunction-associated steatotic liver disease (MASLD).

STUDY DESIGN: Single center, single-blind parallel randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size, short duration, and randomization concerns)

BRIEF BACKGROUND INFORMATION: MASLD is one of the most common liver conditions worldwide, and is treated primarily with lifestyle changes such as diet, weight loss, and physical activity. Citrus fruits like oranges are rich in flavonoids, phytochemicals with antioxidant and anti-inflammatory properties, shown to improve metabolic health. This study aimed to evaluate the effect of daily consumption of whole oranges on hepatic steatosis and metabolic markers in adults with MASLD.

PATIENTS: Adults with MASLD

INTERVENTION: Consumption of whole oranges

CONTROL: Consumption of non-citrus fruits

PRIMARY OUTCOME: Hepatic steatosis prevalence

Secondary Outcome: Fibrosis, liver enzymes, metabolic markers

METHODS (BRIEF DESCRIPTION):

- 62 patients (31 men and 31 women) 30–65 years old with MASLD with sedentary lifestyle and stable weights were recruited at an Italian gastroenterology clinic.
- Inclusion criteria included BMI >25, type 2 diabetes, or metabolic syndrome; stable weight for at least two months; and exercise <1 hour per week for at least six months.

- Patients with chronic inflammatory diseases, other gastrointestinal disorders, malignancy, anticoagulant use, or special diets were excluded.
- MASLD was diagnosed using a Controlled Attenuation Parameter (CAP) score, a measure of liver steatosis that is assessed with transient elastography (FibroScan). A CAP score >275 dB/m indicates MASLD. Transient elastography was also used to diagnose fibrosis.
- Patients were randomly assigned to the intervention group eating 400 g daily of whole “Navelina” oranges or the control group eating 400 g daily of non-citrus fruits like apples, pears, or bananas, for four weeks.
- Patients were given diet guidelines to avoid alcohol, caffeine, and additional vitamin C intake. Assessors provided weekly phone call check-ins to verify stable diet and exercise practices.
- The primary outcome was measured using transient elastography (Fibroscan) to evaluate CAP (steatosis) and liver stiffness for fibrosis by blinded technicians.
- Secondary outcomes included liver enzymes (ALT, AST, alkaline phosphatase), lipids, glucose/insulin markers, C-reactive protein (CRP), and body composition, weight, waist circumference.

INTERVENTION (# IN THE GROUP): 31

COMPARISON (# IN THE GROUP): 31

FOLLOW-UP PERIOD: Four weeks

RESULTS:

Primary Outcome –

- Orange consumption decreased the prevalence of liver steatosis compared to non-citrus fruits (71% vs 100%, respectively; absolute risk reduction [ARR] 29%; $P < .004$).

Secondary Outcome –

- Orange consumption did not improve liver fibrosis, liver enzymes, or metabolic markers compared to non-citrus fruits.
- Orange consumption reduced plasma gamma-glutamyl transferase (GGT) levels compared to non-citrus fruits (mean difference [MD] -4.9 U/L; $P = .05$).

LIMITATIONS:

- The intervention had a short duration and small sample size, limiting the statistical power and the ability to predict sustained treatment outcome.
- Participants were unable to be blinded to the treatment due to the study design.
- Liver health was assessed using transient elastography (FibroScan) without biopsy confirmation of steatosis or fibrosis.
- Treatment and control groups were significantly different in regard to baseline GGT (control group had lower baseline GGT).
- Baseline CAP scores were lower in the treatment group with outcomes categorically considered steatosis if $>275\text{dB/m}$ (no comment if this difference was statistically significant).

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