GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Non-Antibiotic Alternative for Treatment of Bacterial Vaginosis

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Efficacy of Dequalinium Chloride vs Metronidazole for the Treatment of Bacterial Vaginosis: A Randomized Clinical Trial

Raba G, Durkech A, Malík T, et al. Efficacy of Dequalinium Chloride vs Metronidazole for the Treatment of Bacterial Vaginosis: A Randomized Clinical Trial. *JAMA Netw Open.* 2024;7(5):e248661. Published 2024 May 1. doi:10.1001/jamanetworkopen.2024.8661

KEY TAKEAWAY: Dequalinium chloride is non-inferior to metronidazole with comparable cure rates and better tolerability.

STUDY DESIGN: Multicenter, triple-blind, double-dummy noninferiority randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Bacterial vaginosis (BV) is caused by disruption to normal vaginal flora and is implicated in 40–50% of vulvovaginitis cases. The first-line treatment is metronidazole and clindamycin. With antibiotic resistance on the rise, nonantibiotic treatments should be explored. This study investigated the noninferiority of dequalinium chloride.

PATIENTS: Women diagnosed with BV

INTERVENTION: Dequalinium chloride

CONTROL: Metronidazole tablet

PRIMARY OUTCOME: Non-inferiority

Secondary Outcome: BV cure rate, time to resolution, patient tolerability

METHODS (BRIEF DESCRIPTION):

- The patient population was premenopausal women ≥18 years old with four positive Amsel criteria leading to the diagnosis of bacterial vaginosis.
- Researchers provided patients with double-dummy medication kits containing vaginal tablets taken daily for six days (either 10 mg dequalinium chloride or placebo) and oral tablets taken twice daily for seven days (either 500 mg metronidazole or placebo).
- An independent contractor assembled kits and randomized the list so that each kit contained a placebo and active medication. Therefore, patients and providers were blinded.
- After starting treatment at the initial visit, patients had an initial follow-up visit at 7–10 days and a second follow-up visit between 20–40 days.
- Researchers set the non-inferiority margin at 15%, with all calculations done by a blinded statistician.
- Treatment adherence was measured by the number of tablets returned.
- Clinical cure was defined as resolution of abnormal vaginal discharge, negative whiff test, and no clue cells present.
- Clinical improvement was defined as two or more negative Amsel criteria, with bacteriological cure defined as a Nugent score of ≤3, and time to resolution was calculated from the time that the patient reported no symptoms.
- Investigators rated subjective efficacy and tolerability of treatment separately.

INTERVENTION (# IN THE GROUP): 73

COMPARISON (# IN THE GROUP): 78

FOLLOW-UP PERIOD: 40 days

RESULTS:

Primary Outcome –

- Dequalinium chloride was non-inferior to metronidazole for the cure rate of BV at 7–10 days.
  - Intention to treat (between-group difference –0.5%; 95% CI, –11 to 9.8)
  - Per protocol (between-group difference 2.5%; 95% CI, –9.4 to 14)

Secondary Outcome –

- More patients taking dequalinium rated tolerability as “very good” compared to patients taking metronidazole (60% vs 39%, respectively; *P*=.03).
- Clinical cure rates did not differ between dequalinium and metronidazole (93% vs 93%, respectively).
- Time to clinical resolution did not differ between dequalinium and metronidazole (6.7 days vs 6.5 days, respectively).

LIMITATIONS:

- The small sample size, short follow-up interval, and homogenous white European patient population limit the generalizability of the results.

- The study was conducted in Eastern Europe and dequalinium chloride is not available in the United States.

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Imaging Accurately: The Cost of Omitting Contrast in Abdominal CT Scans

Diagnostic Accuracy of Unenhanced Computed Tomography for Evaluation of Acute Abdominal Pain in the Emergency Department

Shaish H, Ream J, Huang C, et al. Diagnostic Accuracy of Unenhanced Computed Tomography for Evaluation of Acute Abdominal Pain in the Emergency Department. *JAMA Surg.* 2023;158(7):e231112. doi:10.1001/jamasurg.2023.1112

KEY TAKEAWAY: Unenhanced computed tomography (CT) for diagnosis of acute abdominal pain in the emergency room is less accurate than CT with contrast.

STUDY DESIGN: Retrospective diagnostic study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Abdominal pain is a common chief concern for presentation to the emergency department (ED). Accurate diagnosis is essential for safe and effective treatment, but this must be balanced with the risks of contrast exposure to the patient. This study evaluated the difference in the accuracy of diagnosis between the unenhanced CT and CT with contrast.

PATIENTS: ED visits for abdominal pain

INTERVENTION: Unenhanced abdominal CT scan

CONTROL: Abdominal CT scan with contrast

PRIMARY OUTCOME: Accuracy of primary diagnosis

METHODS (BRIEF DESCRIPTION):

- The study enrolled 201 consecutive adult patients presenting to the emergency department with acute abdominal pain who underwent contrast-enhanced abdominal CT scans.
- Three blinded radiologists interpreted these scans to establish a reference standard.
- Researchers digitally removed the contrast from the CT images.
- Six different blinded radiologists (3 residents and 3 faculty) interpreted the resulting unenhanced CT scans.
- Researchers compared the diagnostic accuracy for the primary diagnosis and calculated the Gwet interrater agreement coefficient.

INTERVENTION (# IN THE GROUP): 201

COMPARISON (# IN THE GROUP): The same 201 patients

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- The sensitivity of unenhanced CTs was 80% compared to CTs with contrast (95% CI, 77–83).
- The specificity unenhanced CTs of was 84% compared to CTs with contrast (95% CI, 81–87).
- The positive likelihood ratio (+LR) of unenhanced CTs was 5.0 compared to CTs with contrast (95% CI, 4.1–6.0).
- The negative likelihood ratio (-LR) of unenhanced CTs was 0.24 compared to CTs with contrast (95% CI, 0.21–0.28).
- Unenhanced CTs had a moderate interrater agreement compared to CTs with contrast (Gwet interrater agreement coefficient 0.58).

LIMITATIONS:

- A small group of radiologists was used, with a moderate interrater agreement
- The study design paid significant attention to comparing faculty diagnosis vs resident diagnosis, detracting from the primary objective of the study.
- The authors did not report sensitivity, specificity, +LR, and -LR explicitly, although they supplied the raw data to calculate these measures in the eTable.
- Including actionable secondary diagnoses in the overall accuracy statistics artificially decreases the overall diagnostic accuracy of the primary outcome (correct primary diagnosis).

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Low-Dose Calcium Supplementation Clearly Cuts Down on Preeclampsia but Not Preterm Births

Two Randomized Trials of Low-Dose Calcium Supplementation in Pregnancy

Dwarkanath P, Muhihi A, Sudfeld CR, et al. Two Randomized Trials of Low-Dose Calcium Supplementation in Pregnancy. *N Engl J Med.* 2024;390(2):143-153. doi:10.1056/NEJMoa2307212

KEY TAKEAWAY: Low-dose calcium is non-inferior to high-dose calcium supplementation for the prevention of preeclampsia but produces conflicting outcomes in preventing preterm birth.

STUDY DESIGN: Two double-blinded independent randomized comparison trials

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Calcium supplementation, around 1,500–2,000 mg per day, has been recommended by the World Health Organization (WHO) since 2011 to decrease the risk of preeclampsia. Due to adherence and cost concerns from three times a day dosing, this study assessed if 500 mg daily calcium supplementation was as efficacious as 500 mg three times daily dosing.

PATIENTS: Nulliparous pregnant women

INTERVENTION: Low-dose calcium

CONTROL: High-dose calcium

PRIMARY OUTCOME: Preeclampsia and preterm birth rates

METHODS (BRIEF DESCRIPTION):

- Researchers recruited 11,000 primiparous women >18 years old who were <20 weeks gestation in India & Tanzania, with plans to stay in the trial area for six months.
- Exclusion criteria included: History, signs, or symptoms of nephrolithiasis; history of parathyroid disorder or thyroidectomy; had a disease for which digoxin, phenytoin, or tetracycline therapy was indicated.
- Researchers assigned participants at random to receive either one 500 mg elemental oral calcium tablet plus two placebo tablets, or three 500 mg calcium tablets daily through delivery.
- They also recommended that women take vitamin D, 250 IU daily in India, but not in Tanzania.
- The patient's baseline dietary intake was measured through the 24-hour recall method.
- Blood pressure (BP) was measured with an automatic cuff and proteinuria was assessed with a urine dipstick each month during pregnancy, at delivery, and at six weeks postpartum.
- All patients received standard antenatal care per national guidelines.
- Gestational hypertension was defined as systolic BP >140 mmHg, or diastolic >90 on at least two occasions an hour or more apart.
- Severe hypertension was defined as systolic BP >160 or diastolic BP >110 on at least two occasions an hour or more apart.
- Proteinuria: Dipstick at least 1+
- Preterm birth was defined as a live birth before 37 weeks gestation, determined using the best obstetric estimated due date from the last menstrual period (LMP) and ultrasound (US).
- Noninferiority margins for relative risk were 1.5 for preeclampsia and 1.2 for preterm birth.

INTERVENTION (# IN THE GROUP): 11,000

COMPARISON (# IN THE GROUP): 11,000

FOLLOW-UP PERIOD: Nine months

RESULTS:

Primary Outcome –

- Low-dose calcium was non-inferior to high-dose calcium supplementation in the prevention of preeclampsia.
  - India (preeclampsia rate 3.0% vs 3.6%; relative risk [RR] 0.84; 95% CI, 0.68–1.0)
  - Tanzania (preeclampsia rate 3.0% vs 2.7%; RR 1.1; 95% CI, 0.88–1.4)
- Low-dose calcium was non-inferior to high-dose calcium supplementation in the preterm birth rate in India (12% vs 13%; RR 0.89; 95% CI, 0.8–0.98).
- Low-dose calcium was inferior to high-dose calcium supplementation in the preterm birth rate in Tanzania (10% vs 9.7%; RR 1.1; 95% CI, 0.95–1.2).

LIMITATIONS:

- Trials were conducted in only two population groups.

- Some possibility of misclassification for preterm birth due to gestational age assessment based on LMP and US.
- The 24-hour recall method of dietary intake was subject to variation.
- There was no placebo group with no calcium supplementation.
- The study only included nulliparous women.

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Decolonization with Chlorohexidine and Nasal Iodophor

Decolonization in Nursing Homes to Prevent Infection and Hospitalization

Miller LG, McKinnell JA, Singh RD, et al. Decolonization in Nursing Homes to Prevent Infection and Hospitalization. *N Engl J Med.* 2023;389(19):1766-1777. doi:10.1056/NEJMoa2215254

KEY TAKEAWAY: Universal decolonization with over-the-counter topical chlorhexidine for bathing and nasal iodophor in nursing home residents significantly lowered the risk of transfer to the hospital due to infection with relatively simple intervention and a low number needed to treat (NNT).

STUDY DESIGN: Non-blinded, cluster-randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Nursing home residents are at high risk for healthcare-associated infections in part due to older age, chronic wounds, comorbidities, and medical devices. Decolonization programs have shown to be effective in other hospital settings however, this trial aimed to identify the benefit for nursing home residents.

PATIENTS: Nursing home residents

INTERVENTION: Chlorhexidine + nasal iodophor

CONTROL: Routine bathing

PRIMARY OUTCOME: Transfer to a hospital due to infection

Secondary Outcome: Transfer to a hospital for any reasons

METHODS (BRIEF DESCRIPTION):

- 28 skilled nursing facilities in Los Angeles and Orange counties, California were enrolled in the study.
- Nursing homes taking care of pediatric patients, individuals with dementia, or psychiatric patients who had routine decolonization protocols already in use were excluded from the study.
- Demographics:
  - The mean age was 75 years old, 50% were white and 55% were women.
  - Minimum length of stay was 275 days.
  - Additional comorbidities included diabetes, chronic pulmonary lung disease, renal failure, and cancer were similar at baseline.
- Intervention:
  - Chlorhexidine was used for all bathing and showering upon admission and for routine baths.
  - 4% chlorhexidine rinse-off wash for patients who showered, and 2% chlorhexidine no-rinse cloths were used for bed baths.
  - 10% nasal povidone-iodine (nasal iodophor) was administered twice daily for five days after admission and then twice daily for five days every other week.
- Controlled sites used regular bathing techniques.
- There was an 18-month baseline period, a training period, and an 18-month intervention period. The frequency of bathing remained the same for the entire period.
- The number of residents who were transferred to the hospital due to infection was assessed among all residents who had been hospitalized and was measured as the primary outcome.
- The number of residents who were transferred to the hospital for other reasons was assessed among all residents who had been discharged from the nursing home and was measured as the secondary outcome.

INTERVENTION (# IN THE GROUP): 7,338

COMPARISON (# IN THE GROUP): 5,664

FOLLOW-UP PERIOD: 18 months

RESULTS:

Primary Outcome –

- Chlorhexidine + nasal iodophor significantly decreased the risk of transfer to the hospital due to infection compared to routine care (difference in risk ratio [RR] 17%; 95% CI, 11–22; NNT=10).

Secondary Outcome –

- Chlorhexidine + nasal Iodophor decreased the risk of transfer to the hospital for any reason compared to routine care (difference in RR 15%; 95% CI, 9.7–19; NNT=9).

LIMITATIONS:

- Even with dedicated staff training and coaching, three decolonization sites withdrew due to loss of administrative support or effort required to implement decolonization protocols.

- Adherence rates for Iodophor were low.

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Which Anticoagulant for Cancer-Associated Thrombosis?

Comparative Effectiveness of Anticoagulants in Patients with Cancer-Associated Thrombosis

Riaz IB, Fuentes H, Deng Y, et al. Comparative Effectiveness of Anticoagulants in Patients With Cancer-Associated Thrombosis. *JAMA Netw Open.* 2023;6(7):e2325283. Published 2023 Jul 3. doi:10.1001/jamanetworkopen.2023.25283

KEY TAKEAWAY: In adult patients with non-skin cancer-associated thrombosis (CAT), low-molecular-weight heparin (LMWH) is associated with higher rates of venous thromboembolism (VTE) recurrence and all-cause mortality compared to direct oral anticoagulants (DOACs). Additionally, in this population warfarin is also associated with higher rates of VTE recurrence than DOACs, but warfarin and DOACs have similar rates of all-cause mortality.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Management of cancer-associated thrombosis is complicated by the need to balance the risk of venous thromboembolism (VTE) recurrence vs major bleeding due to anticoagulant use, both of which are associated with high mortality. The 2003 CLOT trial, which demonstrated the superiority of parenteral dalteparin (an LMWH) over oral anticoagulants in this patient population, resulted in guideline recommendations for the use of LMWH; however, these results have not been duplicated for other LMWH preparations, and recent randomized clinical trials have found DOACs to be an acceptable alternative. Meanwhile, warfarin use is still prevalent in community practice, raising the need for comparative utilization, efficacy, and safety of these three anticoagulant classes.

PATIENTS: Adults with CAT

INTERVENTION: LMWH and warfarin

CONTROL: DOAC

PRIMARY OUTCOME: VTE recurrence and all-cause mortality

Secondary Outcome: Hospitalization for major bleeding

METHODS (BRIEF DESCRIPTION):

- Adults with CAT, excluding skin cancer, were queried from deidentified administrative claims data from OptumLabs Data Warehouse (OLDW) from January 01, 2012 through September 30, 2019.
- Patients were limited to those who had at least one inpatient or two outpatient visits in a six-month period before VTE diagnosis, filled an anticoagulant prescription within 30 days from the diagnosis date, and had no history of VTE or recent prior oral anticoagulant use.
- Patients were divided into three comparison groups, based on the prescribed anticoagulant (DOAC, LMWH, warfarin) and followed through the end of treatment, which was defined as any one of the following:
  - Anticoagulant discontinuation
  - End of health insurance plan enrollment
  - One year after the VTE index date
  - End of the study period (September 30, 2019)
  - Patient death
- Utilization patterns between the anticoagulant classes were assessed by multinomial logistic regression analysis, accounting for factors such as age, race, cancer type, and VTE type. Sensitivity analyses were then conducted to account for selection bias.
- The three treatment groups were balanced by propensity scoring (PS), and outcomes were calculated as event rates per 100 person-years, with hazard ratios (HRs) calculated with the DOAC group as reference.

INTERVENTION (# IN THE GROUP):

- LMWH: 1,488
- Warfarin: 1,450

COMPARISON (# IN THE GROUP): 2,152

FOLLOW-UP PERIOD: Variable based on the treatment duration (median 1.8–3.2 months)

RESULTS:

Primary Outcome –

- LMWH and warfarin were associated with higher rates of VTE recurrence compared to DOACs:
  - LMWH (hazard ratio [HR] 1.5; 95% CI, 1.1–1.9)
  - Warfarin (HR 1.5; 95% CI, 1.1–1.9)
- LMWH was associated with a higher rate of all-cause mortality compared to DOACs (HR 1.6; 95% CI, 1.2–2.3).

- There was no statistically significant difference between warfarin and DOACs for all-cause mortality (HR 1.2; 95% CI, 0.85–1.7).

Secondary Outcome –

- LMWH was associated with a higher risk of hospitalization for major bleeding compared to DOACs (HR 2.3; 95% CI, 1.6–3.2).
- Warfarin was not associated with a statistically significant different risk of hospitalization for major bleeding compared to DOACs.

LIMITATIONS:

- Due to using claims data, there is potential information bias due to data omissions or inaccuracies in billing or ICD coding.
- The patient population was limited to the United States and did not capture patients who were uninsured or receiving federal or state-regulated insurance, limiting the ability to extrapolate the study findings more broadly.
- Patient adherence markers used in the study are not necessarily reflective of actual medication adherence, potentially confounding clinical events data.

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Does Liraglutide Prevent Peripheral Artery Disease in Patients with Type 2 Diabetes?

Liraglutide for Lower Limb Perfusion in People with Type 2 Diabetes and Peripheral Artery Disease: The STARDUST Randomized Clinical Trial

Caruso P, Maiorino MI, Longo M, et al. Liraglutide for Lower Limb Perfusion in People With Type 2 Diabetes and Peripheral Artery Disease: The STARDUST Randomized Clinical Trial. *JAMA Netw Open.* 2024;7(3):e241545. Published 2024 Mar 4. doi:10.1001/jamanetworkopen.2024.1545

KEY TAKEAWAY: In patients with type 2 diabetes (T2DM) and peripheral arterial disease (PAD), daily liraglutide increased transcutaneous partial pressure of oxygen ($TcPO_2$) significantly more than conventional medical management, which may have implications for wound healing and risk of future amputations.

STUDY DESIGN: Randomized clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: People living with diabetes are at increased risk of developing lower extremity wounds and may eventually require lower extremity amputation due to comorbid PAD. However, few studies have examined how to lower the incidence and reduce the progression of PAD leading to chronic wounds and amputation.

PATIENTS: Adults with T2DM and PAD

INTERVENTION: Subcutaneous liraglutide

CONTROL: Conventional treatment of cardiovascular risk factors

PRIMARY OUTCOME: Measurement of $TcPO_2$

METHODS (BRIEF DESCRIPTION):

- This study was conducted at the University of Campania in Naples Italy.
- Inclusion criteria:
  - Adults ≥35 years old with T2DM and PAD
  - T2DM defined as HbA1C control (6.5–8%) while on a stable dose of glucose-lowering medications
  - HbA1c 6.5–8% while on a stable dose of hypoglycemic medications
  - PAD is defined as $TcPO_2$ of the foot ranging from 30–49 mmHg, as evaluated through transcutaneous oximetry at the medial malleolus and the dorsum of the foot bilaterally. The lowest value was used for the analysis.
- Exclusion criteria:
  - Current or recent (within the last 3 months) use of GLP1 or DPP4 inhibitors
  - Current pregnancy or plans for pregnancy
  - Acute cardiovascular or cerebrovascular events within 14 days of beginning the trial
- A computer-generated random number sequence performed randomization.
- Liraglutide 0.6 mg was given once daily with titration up weekly by 0.6 mg to a target dose of 1.8 mg daily.
- Usual medical management addressing cardiovascular risk factors for PAD including optimization of blood pressure (BP) and cholesterol was used as the control.
- The primary outcome was a 10% difference in TcPO2 at six months, as a marker of clinically significant improvement in PAD severity which may reflect the likelihood of wound healing.

INTERVENTION (# IN THE GROUP): 27

COMPARISON (# IN THE GROUP): 28

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Liraglutide increased the incidence of a 10% increase in $TcPO_2$ compared to the control group (89% vs 46%, respectively; relative risk [RR] 1.9; 95% CI, 1.3–2.9).

LIMITATIONS:

- Small sample size
- The study population was predominately white males and may not be generalizable to the broader population of diabetic patients.
- Limited length of follow-up; it is unclear if the effects of liraglutide have continued beneficial effects long term.

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Preeclampsia: An Independent Risk Factor for Venous Thromboembolism

Preeclampsia and Long-Term Risk of Venous Thromboembolism

Havers-Borgersen E, Butt JH, Johansen M, et al. Preeclampsia and Long-Term Risk of Venous Thromboembolism [published correction appears in JAMA Netw Open. 2024 Jan 2;7(1):e2354306. doi: 10.1001/jamanetworkopen.2023.54306]. *JAMA Netw Open.* 2023;6(11):e2343804. Published 2023 Nov 1. doi:10.1001/jamanetworkopen.2023.43804

KEY TAKEAWAY: Preeclampsia is independently associated with an increased long-term risk of developing a venous thromboembolism (VTE).

STUDY DESIGN: Observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: VTE during pregnancy is one of the leading causes of maternal morbidity and mortality. Although some studies have shown an association between preeclampsia and increased VTE risk in the peripartum and postpartum period, none have examined preeclampsia alone as an independent risk factor for VTE.

PATIENTS: Primiparous adult women

INTERVENTION: Diagnosis of preeclampsia

CONTROL: No preeclampsia

PRIMARY OUTCOME: VTE incidence in women with preeclampsia, VTE diagnosis depending on late vs early diagnosis of preeclampsia

Secondary Outcome: All-cause mortality, mortality in women with preeclampsia with VTE compared to women without preeclampsia and with VTE, and compared to women with preeclampsia without VTE.

METHODS (BRIEF DESCRIPTION):

- The study was conducted in Denmark.
- Patient information, including demographics, and detailed hospital admission information, was obtained from five national patient registries from 1997–2016.
- Patients were included in the study if they were primiparous with no prior history of VTE.
- Patients were excluded if they had a history of VTE.
- Baseline patient demographics in the study included a median age of 28 years old, a slightly higher occurrence of comorbidities (diabetes, chronic hypertension), cesarean deliveries, and multiple birth pregnancies in the pre-eclampsia group.
- Included patients were followed from the start of their pregnancy until VTE development, emigration, or the end of the study.
    - Experimental group patients included those who developed preeclampsia in their primiparous pregnancy and may or may not have developed recurrent preeclampsia in subsequent pregnancies.
- Patients met the criteria for preeclampsia only if they had a diagnosis of preeclampsia, eclampsia, or hemolysis, elevated liver enzymes, low platelets(HELLP) syndrome in their record, as defined by corresponding ICD-10 codes.
- VTE diagnosis data was also obtained from ICD-10 codes that included the development of a pulmonary embolism (PE), deep vein thrombosis (DVT), or both.
- Other VTE risk factors, such as older age, obesity, thrombophilia, venous insufficiency, heart failure (HF), inflammatory and autoimmune diseases, and cancer, were analyzed as covariates. These variables were used to calculate the adjusted hazard ratio (HR).
- Supplemental analysis was performed to evaluate VTE risk in three separate time periods: (1) antepartum, (2) during the six-week postpartum period (puerperium), and (3) after the puerperium.
    - Patients who developed VTE, died, or emigrated before the end of the pregnancy or before the end of the puerperium period were excluded from the VTE analysis of time periods two and three.
- Additional analysis also evaluated VTE incidence in early-onset preeclampsia (birth at <34 weeks gestation) vs late-onset preeclampsia (birth ≥34 weeks gestation).
- Mortality was defined as maternal death from any cause during the follow-up period.
- VTE incidence rates (IR) and all-cause mortality were reported as the number of events per 1,000 person-years.

INTERVENTION (# IN THE GROUP): 23,330

COMPARISON (# IN THE GROUP): 499,215

FOLLOW-UP PERIOD: Median 10 years

RESULTS:

Primary Outcome –

- Women with preeclampsia had a higher VTE incidence compared to women without preeclampsia (IR 1.2 vs 0.85 person-years, respectively; adjusted HR 1.4; 95% CI, 1.3–1.6).
- VTE risk was higher in women with preeclampsia for all three pregnancy periods compared to the control.
  - Antepartum (adjusted HR 2.2; 95% CI, 2.0–2.5)
  - Puerperium (adjusted HR 1.5; 95% CI, 1.3–1.7)
  - Post-puerperium (adjusted HR 1.4; 95% CI, 1.2–1.6)
- There was a higher incidence of VTE in patients diagnosed with early-onset preeclampsia compared to those with late-onset pre-eclampsia (2.5% vs 1.1%, respectively; 95% CI not available).

Secondary Outcome –

- Mortality was higher in women with preeclampsia compared to those without preeclampsia (IR 0.48 vs 0.35 per 1,000 person-years, respectively; adjusted HR 1.4; 95% CI, 1.1–1.6).
- Mortality risk was similar in women with preeclampsia who developed VTE compared to women without preeclampsia who developed VTE (3.1% vs 3.4%, respectively; adjusted HR 0.92; 95% CI, 0.47–1.8).
- Mortality risk was higher in women with preeclampsia who developed VTE compared to women with preeclampsia who did not develop VTE (3.1% vs 0.5%, respectively; adjusted HR 5.5; 95% CI, 2.7–11).

LIMITATIONS:

- This study was limited to primiparous women and did not evaluate the association of preeclampsia and VTE in multiparous women.
- Thrombophlebitis and DVT were grouped in the outcome of “deep vein thrombosis” since they are in the same spectrum of disease, however, this could have led to overdiagnosis of DVT in this study.
- Information regarding potential VTE risk factors to include family history, postpartum contraception use, and history of immobilization was not available to researchers.
- Women in the preeclampsia group had a higher rate of cesarean section deliveries, which may have increased their risk of developing VTE in the puerperium period.
- The design of this study as an observational cohort study limits the assessment of cause-effect relationships between variables and outcomes.

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