GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of October 17 - 21, 2022

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Hormonal Therapy after Surgery for Endometriosis: Decreased Pain and Increased Fertility

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Pre- and Postsurgical Medical Therapy for Endometriosis Surgery

Chen I, Veth VB, Choudhry AJ, et al. Pre-and postsurgical medical therapy for endometriosis surgery. *Cochrane Database Syst Rev*. 2020;11(11):CD003678. Published 2020 Nov 18. doi:10.1002/14651858.CD003678.pub3

KEY TAKEAWAY: In the treatment of endometriosis, surgery followed by hormonal suppression therapy decreases pain recurrence and increases pregnancy rates compared to surgery alone.

STUDY DESIGN: Systematic review of 25 randomized control trials (N=3,378)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Endometriosis is a disease characterized by endometrial tissue outside of the uterine cavity which may cause dysmenorrhea, dyspareunia, pelvic pain, and infertility. It is definitively diagnosed by laparoscopy, and there are two mainstays of treatment: hormone-based medical therapy and surgical excision.

PATIENTS: Women with endometriosis

INTERVENTION: Hormonal medical management with surgery

CONTROL: Surgery alone

PRIMARY OUTCOME: Pain, recurrence of disease

Secondary Outcomes: Pregnancy rates, adverse events

METHODS (BRIEF DESCRIPTION):

- Six databases and other electronic sources were queried (for clinical trials and articles not published in major databases) for RCTs examining the use of suppressing hormone therapy (including GnRHas, danazol, letrozole, progestogens, or combined OCP; excluded LNG-IUD) for treatment of endometriosis before, after, or before and after surgical treatment.
  - Medical therapy was used for at least three months.
  - Medical therapy with analgesics, anti-inflammatory medications, antibiotics, or alternative/dietary interventions were excluded.
- Study population: Women of reproductive age undergoing therapeutic surgical intervention for endometriosis that preserved the pelvic organs.
  - Excluded were those undergoing laparoscopy without a therapeutic intervention, and those who received a hysterectomy.
- Articles that included patients who met the inclusion criteria were examined and outcomes were compiled and evaluated.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: 12 months

RESULTS:

Primary Outcomes –

- Postsurgical medical management decreased pain recurrence more than surgery alone (5 trials, N=657; RR 0.70; 95% CI, 0.52–0.94).
- Presurgical medical therapy yielded no difference in recurrence of pain or disease compared to postsurgical medical management or surgery alone (2 trials, N=326; RR 1.4; 95% CI, 0.95–2.1 & one study, N=273; RR 1.3; 95% CI, 0.97–1.7, respectively).

Secondary Outcomes –

- Post-surgical medical management increased pregnancy rates more than surgery alone (11 trials, N=955; RR 1.2; 95% CI, 1.02–1.4).
- Presurgical medical therapy yielded no difference in pregnancy rates compared to postsurgical medical management or surgery alone.
- There were no serious adverse events reported in any of the studies.

LIMITATIONS:

- Most studies were low or very low quality with small sample sizes.
- Pain is a subjective measurement of disease.
- Multiple types of hormonal medical management were used with results not differentiated based on type of hormonal management.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

Venous Thromboembolism Rates in Hospitalized Patients with COVID-19 Infection: Does Race / Ethnicity Matter?

A Systematic Review and Meta-analysis of Racial Disparities in Deep Vein Thrombosis and Pulmonary Embolism Events in Patients Hospitalized with Coronavirus Disease 2019

Bhakta S, Erben Y, Sanghavi D, et al. A systematic review and meta-analysis of racial disparities in deep vein thrombosis and pulmonary embolism events in patients hospitalized with coronavirus disease 2019. *J Vasc Surg Venous Lymphat Disord*. 2022;10(4):939-944.e3. doi:10.1016/j.jvsv.2022.03.003

KEY TAKEAWAY: Venous thromboembolism rates appear similar between Black/African American and White adult patients hospitalized with COVID-19 infection, yet important limitations must be considered.

STUDY DESIGN: Systematic review of 11 retrospective studies including 10 cohort and one case control study; meta-analysis of six cohort studies (N=9,723)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients hospitalized with COVID-19 infection experience poorer clinical outcomes when they develop venous thromboembolism (VTE). Throughout the COVID-19 pandemic several sources have reported worse outcomes for certain races / ethnicities, specifically Black / African Americans compared with Whites. Yet the true incidence of rates of VTE in different races/ethnicities for patients hospitalized with COVID-19 infections has not been consistently communicated.

PATIENTS: Adults hospitalized with COVID-19 infection

INTERVENTION: Comparing race/ethnicity demographic groups

CONTROL: Not applicable

PRIMARY OUTCOME: Rate of VTE events

METHODS (BRIEF DESCRIPTION):

- The literature review and meta-analysis were conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.
- A broad range of search terms encompassing various VTE presentations and racial/ethnic categorizations were utilized.
- Five studies in the meta-analysis were from the U.S. and one was from the U.K.
- All but one study in the meta-analysis reported utilizing thromboprophylaxis or anticoagulation in their hospitalized patients.
- Although the primary outcome was to assess rate of VTE events across various racial groups/ethnicities, the variance in how racial groups/ethnicities were reported allowed only for comparison between Black/African American and White patients.

INTERVENTION (# IN THE GROUP): N/A

COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: Not available

RESULTS:

- There was no difference between the rates of VTE in Black / African American and White patients hospitalized with COVID-19 infection (*P*=.13).
  - 7% (95% CI, 0 – 10%) Black / African American patients (232 of 4,651)
  - 4% (95% CI, 0 – 7%) White patients (175 of 5,072)

LIMITATIONS:

- The lack of uniform standards for the reporting of race/ethnicity creates limitations as there is not a way to correct for any confounding bias it introduces.
- The possibility of underdiagnosed VTE in mortality statistics related to various socioeconomic factors must be considered.
- Similarly, without more in-depth knowledge regarding the extent of racial and socioeconomic inequalities exposed by the COVID-19 pandemic, this systematic review may be seriously under-powered.

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Earlier CPAP Appears to Reduce Risk of Intubation in Patients with Acute Hypoxic Respiratory Failure Due to COVID-19 Pneumonia

Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients with Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial

Perkins GD, Ji C, Connolly BA, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients with Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. *JAMA*. 2022;327(6):546-558. doi:10.1001/jama.2022.0028

KEY TAKEAWAY: Prompt initiation of CPAP instead of continuing conventional O_2 therapy may reduce rates of intubation and 30-day mortality in patients with acute hypoxic respiratory failure secondary to COVID-19 pneumonia and increasing oxygen requirements after more than seven days of symptoms.

STUDY DESIGN: Parallel group, non-blinded, multi-site randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The COVID-19 pandemic has placed immense strain on healthcare resources, especially intensive care bed availability. An optimal strategy for ventilatory support is still being elucidated. This study examined whether the results of previous small-scale studies suggesting high-flow nasal oxygen or CPAP might decrease risk of intubation and ICU admission or 30-day mortality and could be replicated in a larger population.

PATIENTS: Adults with acute hypoxic respiratory failure secondary to COVID-19 pneumonia

INTERVENTION: CPAP or high flow nasal oxygen

CONTROL: Conventional nasal cannula oxygen

PRIMARY OUTCOME: Composite of tracheal intubation or mortality within 30 days

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: Hospitalized adult patients with known or suspected COVID-19 and acute hypoxic respiratory failure (defined as SpO_2 of 94% or less despite a minimum FiO_2 of 0.40), and who were eligible for intubation if needed.
- Exclusion criteria: Need for invasive ventilation within one hour, pregnancy, or planned withdrawal of treatment
- Subjects randomized by an internet-based system with allocation concealment.
- Data were collected throughout hospital stay as well as from national datasets to minimize loss to follow up; data collected at randomization included demographics, comorbidities, and vital signs.
- Decisions regarding treatment discontinuation and intubation were individualized by the treating clinicians based on local protocols and available resources.
- Primary analysis was unadjusted.
- Secondary analysis of tracheal intubation in 30 days, mortality in 30 days, median time to intubation, duration of invasive ventilation, time to death, and length of stay in hospital or ICU were adjusted for age, sex, BMI >35, race and ethnicity, FIO_2, respiratory rate, and treatment phases, with hospital site included as a random effect. Exploratory analysis was performed via inverse probability weighting to limit confounding effects of study crossover.

INTERVENTION (# IN THE GROUP):

- CPAP: 377
- High Flow Nasal Oxygen: 415

COMPARISON (# IN THE GROUP): 468

FOLLOW UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- Early CPAP decreased composite rate of intubation or mortality within 30 days compared to conventional oxygen therapy (36% vs 44%; absolute difference −8%; 95% CI, −15% to −1%).
- Early HFNC did not change the composite rate of intubation or mortality within 30 days compared to conventional oxygen therapy (44% vs 45%, absolute difference −1%, 95% CI, −8% to 6%).

Secondary Outcomes –

- Early CPAP decreased the rate of intubation and the rate of ICU admission within 30 days (33% vs 41%, absolute difference −8%, 95% CI, −15% to −1%).
- Early CPAP increased the time to intubation compared to control (2.0 days vs 1.0 days; absolute difference 1.0 day; 95% CI, 0.2 to 1.8 days).
- Neither intervention significantly altered 30-day mortality compared to control (CPAP: 17% vs 19%; absolute difference −3%; 95% CI, −8% to 3%; HFNC: 19% vs 20%; absolute difference −1%; 95% CI, −7% to 4%).

- The CPAP group had a higher rate of adverse events than the other two groups. Four patients had serious adverse events, and all of these were in the CPAP group; three of these patients developed pneumomediastinum and one had vomiting requiring emergent intubation.

LIMITATIONS:

- Patients, clinicians, and data analysts were unable to be blinded given nature of intervention.
- Significant cross-over due to site-dependent therapy availability.
- COVID-19 variants were not sequenced, which may limit cross-applicability to new variants with different pathogenicity.
- May have been underpowered to detect benefit of HFNC.
- May have been underpowered to detect differences in the primary outcome in non-white patients, patients over age 50 years, obese patients, and patients randomized within seven days of symptom onset.

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Is Glyburide a Safer Pharmacological Option Compared to Insulin When Managing Gestational Diabetes?

Association of Glyburide and Subcutaneous Insulin with Perinatal Complications Among Women with Gestational Diabetes

Hedderson MM, Badon SE, Pimentel N, et al. Association of Glyburide and Subcutaneous Insulin with Perinatal Complications Among Women with Gestational Diabetes [published correction appears in *JAMA Netw Open*. 2022 Apr 1;5(4):e2212571]. *JAMA Netw Open.* 2022;5(3):e225026. Published 2022 Mar 1. doi:10.1001/jamanetworkopen.2022.5026

KEY TAKEAWAY: Overall, there is no significant difference in perinatal complications between continuous exposure to glyburide or subcutaneous insulin when treating gestational diabetes (GDM). Glyburide may reduce the risk of respiratory distress and NICU admission.

STUDY DESIGN: Population-based cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: GDM affects roughly 10% of all pregnancies in the United States. Nearly half of women diagnosed with GDM during pregnancy require pharmacologic therapy to obtain glycemic control. The American Diabetes Association (ADA) and American College of Obstetrics and Gynecology (ACOG) recommend insulin as the first line treatment option for GDM. Current recommendations endorsed by these organizations include avoiding glyburide, due to safety and efficacy concerns concluded from prior limited studies.

PATIENTS: Pregnant women with new onset gestational diabetes

INTERVENTION: Glyburide

CONTROL: Subcutaneous insulin

PRIMARY OUTCOME: Perinatal, neonatal, and maternal outcomes

METHODS (BRIEF DESCRIPTION):

- Nulliparous women with singleton pregnancies diagnosed with GDM that failed medical nutrition therapy and initiated on glyburide or subcutaneous insulin were identified.
- Exclusion criteria: Pre-existing type 2 diabetes mellitus (T2DM), T2DM diagnosed during pregnancy, taking metformin or other diabetic medications without diagnosis of GDM, initiated on medication prior to GDM diagnosis and multiple pregnancies.
- Possible confounders were identified and adjusted for during analysis using propensity scoring. The possible confounders included: maternal age, medical history, substance use (smoking, alcohol), race/ethnicity, glycemic control, and GDM screening glucose values as a marker of severity.
- The mean maternal age was 32 years old with a pre-pregnancy BMI in the overweight to obese range.
- Participants were categorized into either the sustained glyburide or subcutaneous insulin group. Participants could be transitioned to other treatment modalities. Those that remained on initial therapy were categorized into the per-protocol (PP) arm of the study. While the participants that changed medications were categorized to the intention-to-treat (ITT) arm. The PP arm of the study aimed to estimate the effect of sustained exposure, while ITT aimed to estimate the effect of initiating each therapy.
- A prescription medication database was monitored every seven days for prescription refills to determine categorical exposure level to each therapy for PP analysis.
- Participants kept glucose logs, recording fasting and one–hour postprandial capillary glucose readings daily.
- After delivery perinatal, neonatal, and maternal outcomes were assessed. The outcomes of interest included neonatal hypoglycemia, jaundice, shoulder dystocia, respiratory distress, NICU admission, birthweight-for-gestational age, and cesarean delivery.

INTERVENTION (# IN THE GROUP): 8,845

COMPARISON (# IN THE GROUP): 707

FOLLOW UP PERIOD: Through delivery

RESULTS:

- Glyburide reduced the risk of neonatal distress by 2.0 per 100 births compared to insulin (95% CI, 0.13–3.9).
- Glyburide reduced the risk of NICU admission by 3.3 per 100 births compared to insulin (95% CI, 0.2–6.45).
- There was no risk difference between glyburide and insulin in the following outcomes: cesarean delivery, neonatal hypoglycemia, jaundice, shoulder dystocia, large-for-gestational age.

LIMITATIONS:

- Exposure dose was not considered or investigated in this study.

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