GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 2 - Issue 13

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of March 28 - April 1, 2022

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- IBS and Probiotics: Do Probiotics Really Help?
- Induction during Pregnancy: Buprenorphine Can Be Started at Home

COVID-19 Affects All: A Review of How Maternal and Child Health Have Been Impacted by the Pandemic

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis

Chmielewska B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis [published correction appears in Lancet Glob Health. 2021 Jun;9(6):e758]. *Lancet Glob Health*. 2021; 9(6):e759-e772. doi:10.1016/S2214-109X(21)00079-6

KEY TAKEAWAY: Maternal and fetal outcomes including maternal deaths, stillbirths, ruptured ectopic pregnancies, and maternal depression have worsened during the COVID -19 pandemic.

STUDY DESIGN: Systematic review and meta-analysis of 40 cohort studies (N= 3,302,547)

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: COVID-19 has affected many aspects of the healthcare system and across all patient populations. This systematic review looks at the effects of the COVID-19 pandemic on maternal and infant health during and after pregnancy. The impact of the pandemic is not limited to the direct effects of the disease, but also the disruption of the healthcare infrastructure and access to resources.

PATIENTS: Pregnant females and neonates

INTERVENTION: Pregnancy during COVID-19 pandemic

CONTROL: Pregnancy prior to COVID-19 pandemic

OUTCOME: Maternal death, stillbirth, neonatal death, maternal morbidity, surgical treatment of ectopic pregnancies, delivery outcomes, preterm birth, PPH, and neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- Comprehensive literature review of studies on maternal and neonatal outcomes during the COVID-19 pandemic
  - 40 studies were included in the qualitative synthesis, 31 studies in the meta-analysis. Pregnant females from 17 different countries were included.
  - Studies were published January 1, 2020–January 8, 2021
- All included studies compared pregnancy outcomes before vs during the COVID-19 pandemic
  - Delivery outcomes: vaginal, cesarean, instrumental, induction of labor
  - Neonatal outcomes: low APGAR, low birth weight, NICU admission
- Mantel – Haenszel method was used to generate a random-effect estimate of the pooled odds of each outcome.
- Newcastle Ottawa Scale was used to score each study based on the selection of study groups, comparability of groups and ascertainment of outcome of interest.
- Maternal depression was measured with the Generalized Anxiety and Depression Scale, EPDS (scale 0–30, higher scores indicating worse symptoms), GAD7, PHQ9, Symptom checklist 90 Revised, and Inventory of Depression and Anxiety Symptoms.

INTERVENTION (# IN THE GROUP): not available

COMPARISON (# IN THE GROUP): not available

FOLLOW UP PERIOD: not available

RESULTS:

- Stillbirths significantly increased during the pandemic (12 studies, N=333,413; pooled OR 1.3; 95% CI, 1.1–1.5).
- Maternal deaths significantly increased during the pandemic (3 studies, N =3,461,877; pooled OR 1.4; 95% CI, 1.2–1.5).
- Ruptured ectopic pregnancies significantly increased during the pandemic (3 studies, N=309; OR 5.8; 95% CI, 2.2–16; I^2=26%).
- Maternal depression, based on EPDS, significantly worsened during the pandemic (3 studies, N=8,847; mean difference 0.42; 95% CI, 0.02–0.81; I^2=79%).
- During the pandemic, there were no significant changes in spontaneous vaginal deliveries, cesarean deliveries, instrumental deliveries, labor inductions, or NICU admissions.

LIMITATIONS:

- Retrospective study design
- Inconsistent definition and reporting of outcomes
- Inconsistency in selection of control groups
- Only 19 studies adjusted for socioeconomic status, ethnic background, comorbidities, and confounding factors.

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COVID-19 in Pregnancy: Less Symptoms, More Severe Illness

Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ.* 2020; 370:m3320. Published 2020 Sep 1. doi:10.1136/bmj.m3320

KEY TAKEAWAY: Pregnant and recently pregnant patients with COVID-19 are at a greater risk for adverse maternal and neonatal outcomes compared to those without COVID-19. Pregnant and recently pregnant patients are at a greater risk for ICU admission, invasive ventilation, and ECMO when infected with COVID-19 compared to non-pregnant women; however, they are less likely to experience symptoms.

STUDY DESIGN: Living systematic review and meta-analysis of 192 cohort studies (N=634,657)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Pregnancy is a risk factor for severe COVID-19 infection, though exact prevalence, risk factors, and adverse effects on mothers and infants remains poorly understood. Due to the rapid publication of studies and limited validity across studies, creating guidelines is a challenge. This study synthesizes evolving literature to assist in creating evidence-based recommendations.

PATIENTS: Pregnant and recently pregnant women

INTEVENTION: COVID-19 infection

CONTROL: Non-pregnant reproductive age women with COVID-19; pregnant and recently pregnant women without COVID-19

OUTCOME: Symptoms, maternal outcomes, neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- Weekly systematic searches across major databases, with random effects meta-analysis every 2-4 months
  - 58 of 192 studies (30%) from US.
  - All included women were of reproductive age
- Maternal Outcomes: admission to ICU, invasive ventilation, ECMO
- Neonatal Outcomes: Preterm birth, admission to NICU
- These studies analyzed different outcomes for different comparison groups.
  - Nonpregnant women with COVID-19 vs pregnant or recently pregnant women with COVID-19: symptoms, maternal outcomes
  - Pregnant or recently pregnant women with COVID-19 vs pregnant or recently pregnant women without COVID-19: maternal outcomes, neonatal outcomes
- Diagnosis lab-confirmed, or suspected to have COVID-19 based on clinical or radiologic findings

INTERVENTION (# IN THE GROUP): 64,676

COMPARISON (# IN THE GROUP): 569,981

FOLLOW UP PERIOD: none

RESULTS:

- Pregnant or recently pregnant women with COVID-19 compared to non-pregnant women with COVID-19 were at a higher risk for:
  - ICU admission (7 studies, N=601,108; OR 2.1; 95% CI, 1.5–3.0)
  - Invasive ventilation (6 studies, N=601,044; OR 2.6; 95% CI, 2.3–2.9)
  - ECMO (2 studies, N=461,936; OR 2.0; 95%, CI, 1.2–3.3)
- Pregnant or recently pregnant women with COVID-19 compared to non-pregnant women with COVID-19 were less likely to have symptoms (4 studies, N=462,051; OR 0.28; 95% CI, 0.13–0.62).
- Pregnant or recently pregnant women with COVID-19 compared to pregnant or recently pregnant women without COVID-19 were at a higher risk for:
  - All-cause mortality (8 studies, N=4820; OR 2.9; 95% CI, 1.1–7.5)
  - ICU admission (7 studies, N=4,990; OR 19; 95% CI, 7.5–46)
  - Preterm birth (18 studies, N=8549; OR 1.5; 95% CI, 1.1–1.9)
  - Having a child requiring NICU admission (10 studies, N=5,873; OR 4.9; 95% CI, 1.9–12.8)

LIMITATIONS:

- COVID-19 sampling strategies varied
- Heterogeneity in definition of symptoms, tests, and outcomes

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Considering PHQ-2 and PHQ-9 in Combination to Screen for Major Depression in the Family Medicine Setting

Accuracy of the PHQ-2 Alone and in Combination With the PHQ-9 for Screening to Detect Major Depression Systematic Review and Meta-analysis

Levis B, Sun Y, He C, et al. Accuracy of the PHQ-2 Alone and in Combination With the PHQ-9 for Screening to Detect Major Depression: Systematic Review and Meta-analysis. *JAMA.* 2020; 323(22):2290–2300. doi:10.1001/jama.2020.6504

KEY TAKEAWAY: The PHQ-2 (≥2) alone had the greatest sensitivity and the PHQ-2 (≥3) followed by the PHQ-9 (≥10) had the greatest specificity when screening patients for Major Depressive Disorder (MDD).

STUDY DESIGN: Systematic review and meta-analysis of 100 RCTs (N=44,318)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Routine screening for depression is an important part of providing complete primary medical care. The Patient Health Questionnaire-9 (PHQ-9) is a self-reporting tool used to identify patients with Major Depressive Disorder (MDD). The PHQ-2, containing the first 2 questions of the PHQ-9, is often considered "pre-screening" to determine if the full PHQ-9 should follow. However, it is unknown how accurate the two are independently versus together.

PATIENTS: Patients undergoing screening for MDD

INTEVENTION: PHQ-2 alone or in combination with PHQ-9

CONTROL: PHQ-9 alone

OUTCOME: Accuracy of MDD diagnosis

METHODS (BRIEF DESCRIPTION):

- Data was obtained from a larger systematic review of the PHQ-2, which gathered 100 studies (N=44,318) evaluating the use of the PHQ-2 to screen for MDD in adults.
- Data from each of the participants were used to analyze the separate sensitivity/specificity of:
  - PHQ-2 score alone (using cutoffs of >2 or >3)
  - PHQ-2 ≥2 then PHQ-9
  - PHQ-2 ≥3 then PHQ-9
  - PHQ-9 alone.
- PHQ-2 maximum score is 6 (≥2 indicating increased likelihood of MDD); PHQ-9 maximum score is 27 (≥10 indicating likely diagnosis of MDD)
- This created an unusual circumstance in which all participants were part of both the intervention and comparison groups

INTERVENTION (# IN THE GROUP): 10,627

COMPARISON (# IN THE GROUP): 10,627

FOLLOW UP PERIOD: Two weeks

RESULTS:

- The sensitivity for PHQ-2 (≥2) alone was the highest. The specificity for the PHQ-2 (≥3) followed by the PHQ-9 (≥10) was the highest. However, statistical analysis was not completed.
  - PHQ-9 (score ≥10) alone
    - Sensitivity 0.86; 95% CI, 0.76–0.86
    - Specificity 0.85; 95% CI, 0.82–0.87
  - PHQ-2 (score ≥2) alone
    - Sensitivity 0.92; 95% CI, 0.88–0.95
    - Specificity 0.67; 95% CI, 0.63–0.70
  - PHQ-2 (score ≥3) alone
    - Sensitivity 0.72; 95% CI, 0.67–0.77
    - Specificity 0.85; 95% CI, 0.83–0.87
  - PHQ-2 score ≥2 then PHQ-9 score ≥10
    - Sensitivity 0.82; 95% CI, 0.76–0.86
    - Specificity 0.87; 95% CI, 0.84–0.89
  - PHQ-2 score ≥3 then PHQ-9 score ≥10
    - Sensitivity 0.70; 95% CI, 0.64–0.75
    - Specificity 0.91; 95% CI, 0.89–0.93

LIMITATIONS:

- Numerous studies did not exclude participants who may already be diagnosed with depression prior to screening.
- Studies were excluded if they included college or university recruited participants.
- No statistical analysis between the groups.

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IBS and Probiotics: Do Probiotics Really Help?

Efficacy and Safety of New Lactobacilli Probiotics for Unconstipated Irritable Bowel Syndrome

Oh JH, Jang YS, Kang D, Chang DK, Min YW. Efficacy and Safety of New Lactobacilli Probiotics for Unconstipated Irritable Bowel Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients*. 2019; 11(12):2887. Published 2019 Nov 27. doi:10.3390/nu11122887

KEY TAKEAWAY*: Foodis lactobacillus* probiotic, taken daily, may decrease symptoms and abdominal pain in patients with unconstipated IBS.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Irritable Bowel Syndrome (IBS) is one of the most frequent diagnoses in the evaluation of GI symptoms. Since its treatment can be multifactorial and prolonged, patients often seek a solution for their most urgent symptoms. Probiotics have been considered a possible treatment for symptomatic control while pursuing a multifactorial treatment approach

PATIENTS: Adults with unconstipated IBS

INTERVENTION: *Foodis lactobacillus* probiotic taken daily

CONTROL: Placebo capsule

OUTCOME: IBS

Secondary Outcome: Abdominal pain

METHODS (BRIEF DESCRIPTION):

- Patients were Vietnamese individuals living in Korea with Rome III criteria for unconstipated IBS. They were randomly assigned to intervention or control group.
- Intervention group received the *Foodis lactobacillius* capsule taken daily with water, while the control group received a sham capsule without bacteria.
- Weekly Subject Global Assessment (SGA) and Visual Analogue Scale (VAS) scores were collected to evaluate primary and secondary outcomes, respectively. A blinded investigator collected the results for the same questionnaires after four weeks.
  - A higher SGA score and lower VAS score indicated improvement in symptoms and pain, respectively
  - Score ≥2 (moderately relieved) on >2 of 4 weekly SGA's indicates "responder"
  - ≥30% reduction in VAS scores from baseline for >2 of 4 weeks indicates "responder"
- Outcomes were measured by comparison of the scores in the placebo group and the control group for overall IBS symptom relief (SGA) and abdominal pain (VAS).

INTERVENTION (# IN THE GROUP): 26

COMPARISON (# IN THE GROUP): 24

FOLLOW UP PERIOD: Four weeks

RESULTS:

Primary Outcome –

- *Foodis lactobacillus* group saw a greater improvement in IBS symptoms than the placebo group (81% vs 46%, *P*=.009)

Secondary Outcome –

- The *Foodis lactobacillus* group saw a greater improvement in abdominal pain than the placebo group (69% vs 42%, *P*=.048)

LIMITATIONS:

- The study was under-powered with a small sample size of 50 patients who were Vietnamese living in Korea with different internal microbiomes.
- The participants' diets and external factors (medications, environment, etc.) were not controlled.
- The bacteria used was isolated from Vietnamese patient feces and may not be universally applicable
- There was a loss of statistical significance in improvement by the end of the study period.

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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 Air Force Medical Department, the Air Force at large, or the Department of Defense.

Induction during Pregnancy: Buprenorphine Can Be Started at Home

Home Induction of Buprenorphine for Treatment of Opioid Use Disorder in Pregnancy

Kelly JC, Raghuraman N, Stout MJ, et al. Home Induction of Buprenorphine for Treatment of Opioid Use Disorder in Pregnancy. *Obstet Gynecol*. 2021; 138(4):655–659. doi:10.1097/AOG.0000000000004539

KEY TAKEAWAY: There is proof of concept in home induction of sublingual buprenorphine during pregnancy.
STUDY DESIGN: Retrospective cohort study
LEVEL OF EVIDENCE: STEP 4 (downgraded due to lack of power and no statistical analysis)

BRIEF BACKGROUND INFORMATION: There is a lack of evidence regarding risks and benefits of home induction in pregnant patients. Pregnant patients have unique barriers in their access to care, but particularly benefit from treatment of opioid use disorder (OUD). Home induction of buprenorphine may decrease some of these barriers.

PATIENTS: Pregnant patients with active OUD
INTERVENTION: Buprenorphine induction at home
CONTROL: Observed outpatient induction
OUTCOME: Withdrawal, buprenorphine adherence, abstinence of illicit opioid use, and 3–month treatment retention after induction

METHODS (BRIEF DESCRIPTION):

- Included all patients (n=63) who underwent buprenorphine induction for treatment of OUD during a 2.5 year period.
- Patients self-elected home induction or observed outpatient induction per defined protocols after counseling.
  - Observed induction involved having day one dosed in clinic after COWS scoring with days two to four performed at home with instructions.
  - Home induction had days one to four performed at home with detailed instructions.
- Data were abstracted from the electronic health record and descriptive statistics were used.
- Retention was defined as returning to >75% of monthly return visits.

INTERVENTION (# IN THE GROUP): 55
COMPARISON (# IN THE GROUP): 8

FOLLOW UP PERIOD: 3 months

RESULTS:

- The home induction group had zero cases of precipitated withdrawal while the observed outpatient group had one.
- 60% of patients in the home induction group vs 72% of patients in the observed outpatient group had urine buprenorphine metabolites at 1–week follow up.
- 53% of patients in the home induction group vs 80% in the observed outpatient group tested positive for illicit opiates at the 1–week follow up.
- Three-month retention in treatment was higher in the home induction group (87%) than the observed outpatient group (63%).

LIMITATIONS:

- Inadequate power to compare the efficacy or safety of home vs observed induction.
  - Single-center trial
- Patients not randomized to treatment/control groups; patients undergoing home induction were more likely to be white and to have used opioid agonist therapy in the past.
- Formal comparative statistics between the experimental and control groups were not performed, limiting the application of study results.

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