# GEMs of the Week

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**Week of September 11 - 15, 2023**

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# Picking Up Good Vibrations, to Cure Constipation

**Randomized Placebo-Controlled Phase 3 Trial of Vibrating Capsule for Chronic Constipation**

Rao SSC, Quigley EMM, Chey WD, Sharma A, Lembo AJ. Randomized Placebo-Controlled Phase 3 Trial of Vibrating Capsule for Chronic Constipation. *Gastroenterology*. 2023;164(7):1202-1210.e6. doi:10.1053/j.gastro.2023.02.013



**KEY TAKEAWAY:** Vibrating capsule therapy may present an effective alternative treatment for treating chronic idiopathic constipation.

**STUDY DESIGN:** Randomized Placebo-Controlled Phase 3 Trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** While Chronic Idiopathic Constipation affects a significant proportion of the world, a recent study published in the A*merican Journal of Gastroenterology* shows that as many as 40-50% of patients are dissatisfied with current pharmaceutical options, regardless of whether they are OTC or prescribed treatment. Among new alternative therapies being explored, direct mechanical stimulation of the lower GI tract via a vibrating capsule is a therapy that offers one of the more novel non-pharmaceutical options.

**PATIENTS:** Adults with a diagnosis of idiopathic constipation resistant to osmotic and stimulant laxative treatments

**INTERVENTION:** Vibrating capsule

**CONTROL:** Placebo capsule

**PRIMARY OUTCOME:** Increase in one or more complete spontaneous bowel movements per week

Secondary Outcome: Straining effort, bloating, and stool consistency

**METHODS (BRIEF DESCRIPTION):**

- Multicenter, double-blind, placebo-controlled, clinical trial
- They included adults aged 22 years old and older with chronic idiopathic constipation who reported no relief of symptoms from other available therapies (osmotic and/or stimulant laxatives for at least one month).
- Participants also must have had an average of 1–2.5 SBM (Spontaneous Bowel Movements) per week to be eligible.
- Exclusion criteria included those with significant cardiovascular, GI, or other systematic diseases, patients with a history of bariatric surgery, and pregnant/lactating patients.
- Participants were randomized to receive either vibrating capsules or placebo capsules.
    - They were instructed to take one capsule orally at nighttime (9–10 PM) five times a week (no capsules on Wednesdays and Sundays).
- Treatment efficacy was measured by the amount of CSBMs (Complete Spontaneous Bowel Movements) each patient recorded throughout treatment.
    - When compared to baseline, an increase of one or more CSBMs per week during at least six of the eight weeks of treatment was considered efficacious.
- Along with the amount of CSBMs, stool consistency, straining, and bloating were recorded by patients both in baseline and treatment periods.
    - Stool consistency: Bristol Stool Scale, 1–7
    - Straining effort: Visual analog scale, 0–10 (No straining–unbearable straining)
    - Bloating: Visual analog scale, 0–10 (no bloating–unbearable bloating)

**INTERVENTION (# IN THE GROUP):** 163

**COMPARISON (# IN THE GROUP):** 149

**FOLLOW-UP PERIOD:** 56 days after the first day of treatment

**RESULTS:**

Primary Outcome –

- A greater percentage of patients utilizing the vibrating capsule reported an increase of one or more CSBMs per week as compared to the placebo group (39% vs 22%; *P*=.001).
- A greater percentage of patients in the treatment group also reported an increase of 2 or more CSBMs per week as compared to the placebo group (23% vs 11%; *P*=.008).

Secondary Outcome –

- The treatment group reported a larger average in decrease of straining effort (mean change –1.6 vs –1.0 respectively; mean difference [MD] of change –0.56; 95% CI, –1.0 to –0.12).
- The treatment group reported a larger average increase in the Bristol stool scale (mean increase

0.92 vs 0.44 respectively; MD 0.48; 95% CI, 0.27–0.70).

- There was no significant difference in bloating between treatment and control groups.

**LIMITATIONS:**

- The patient population comprised fewer men than women, limiting the representation of a more general population.
- The trial was limited to eight weeks, without data to test long-term efficacy or safety.

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# Patches for Peanuts? Cutaneous Immunotherapy in Toddler Peanut Allergy Treatment

**Phase 3 Trial of Epicutaneous Immunotherapy in Toddlers with Peanut Allergy**

Greenhawt M, Sindher SB, Wang J, et al. Phase 3 Trial of Epicutaneous Immunotherapy in Toddlers with Peanut Allergy. *N Engl J Med*. 2023;388(19):1755-1766. doi:10.1056/NEJMoa2212895



**KEY TAKEAWAY:** Epicutaneous immunotherapy in toddlers with peanut allergy demonstrated superior desensitization to peanuts compared to placebo.

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

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Peanut allergy affects about 2% of children in the United States (US), can cause anaphylaxis, and frequently persists into adulthood. There are no approved treatments for children under four years old, but given that early consumption of peanuts reduces the risk of peanut allergy, desensitization in these younger children may be especially effective. This study evaluated if patch-based epicutaneous immunotherapy was safe and effective in children 1–3 years old with peanut allergy.

**PATIENTS:** Toddlers with peanut allergy

**INTERVENTION:** Peanut patch

**CONTROL:** Placebo patch

**PRIMARY OUTCOME:** Increased tolerance to peanut protein

Secondary Outcome: Changes in cumulative reactive dose, eliciting dose, and adverse events

**METHODS (BRIEF DESCRIPTION):**

- Children 1–3 years old with a peanut allergy from 51 sites in the US, Australia, Canada, and Europe were enrolled after a screening peanut challenge to determine an eliciting dose that triggered symptoms.
- Children following a peanut-free diet, with peanut-specific IgE level >0.7 kU/L, positive peanut skin prick test with wheal ≥6 mm, and a positive peanut food challenge, with an eliciting dose of ≤300 mg peanut protein, were enrolled.
- Those children with a history of severe anaphylaxis before or during the screening were excluded.
- Participants had a median age of 2.5 years; 68.8% were male, and 63.3% were White.
- Patients were randomized 2:1 to either a peanut or placebo patch applied daily to the interscapular region for 12 months.
- After 12 months of treatment, the food challenge was repeated, with the addition of larger protein doses, to determine the dose of peanut protein eliciting symptoms and the maximum cumulative dose tolerated.
- Positive patient response was met if the baseline eliciting dose was >10 mg of peanut protein and the post-treatment eliciting dose was ≥1000 mg, or if the baseline dose was ≤10 mg and the post-treatment dose was ≥300 mg.
- The percentage of children in each group who reached an eliciting dose ≥1000 mg or cumulative dose ≥3444 mg, regardless of baseline dose, was also measured.

**INTERVENTION (# IN THE GROUP):** 244

**COMPARISON (# IN THE GROUP):** 118

**FOLLOW-UP PERIOD:** 12 months

**RESULTS:**

Primary Outcome –

- A positive patient response was seen in 67% of children in the treatment group, compared to 34% of children in the control (risk difference 34%; 95% CI, 23–45).

Secondary Outcome –

- The eliciting dose at 12 months was ≥1000 mg, regardless of baseline dose, in 64% of patients who received the peanut patch, compared to 30% who received a placebo (risk difference 35%; 95% CI, 24–46).
- The cumulative dose at 12 months was ≥3444 mg in 37% of patients in the treatment group, compared with 10% of patients in the placebo group (risk difference 27%; 95% CI, 18–36).
- Adverse application site reactions were observed in both groups; severe local site reactions were more common in the intervention group.
- Serious adverse events were reported in 21 patients receiving the peanut patch (8.6%) and three receiving placebo (2.5%).

**LIMITATIONS:**

- Patients with a history of severe peanut anaphylaxis were excluded.

- Although similar to other food allergy studies, a lack of racial diversity may limit generalizability.
- The appropriate duration of peanut patch treatment to achieve maximal response is unknown.
- Effects after treatment cessation were not studied.
- There was a higher dropout rate in the peanut patch group.

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# Electronic Health Record Messaging Improves Access to Well Child Care

**Effect of Electronic Outreach Using Patient Portal Messages on Well Child Care Visit Completion: A Randomized Clinical Trial**

Berset AE, Burkhardt MC, Xu Y, Mescher A, Brinkman WB. Effect of Electronic Outreach Using Patient Portal Messages on Well Child Care Visit Completion: A Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(11):e2242853. Published 2022 Nov 1. doi:10.1001/jamanetworkopen.2022.42853



**KEY TAKEAWAY:** Electronic health record (EHR) patient portal messages increase well-child check (WCC) visits.

**STUDY DESIGN:** Randomized clinical trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** The COVID-19 pandemic delayed well child care and vaccination rates services. This study aimed to demonstrate the effectiveness of electronic health record portal messaging to improve rates of well child care and COVID-19 vaccinations.

**PATIENTS:** Pediatric patients

**INTERVENTION:** Tailored and standard messages

**CONTROL:** No messages

**PRIMARY OUTCOME:** Completion of WCC within eight weeks

Secondary Outcome: COVID-19 vaccination within eight weeks in eligible patients

**METHODS (BRIEF DESCRIPTION):**

- Patients were 6–17 years old, mostly Black, non-Hispanics, with public insurance, active EHR portal account, and no WCC in the past year.
- Patients excluded from the study were non-English or Spanish speakers or those receiving outside primary care.
- Interventions consisted of sending out two patient portal messages in two consecutive weeks.
- An email informed parents that the messages had been sent to the portal with a login link to access the message.
- The standard message included the patient's name and, a reminder of the overdue WCC, with a request to schedule through the EHR or via phone call.
- The tailored message included the standard message items, the date of the last WCC, and the patient's age.
- Messages were randomly assigned. All standard messages were sent the first week and tailored messages were sent the following week.
- Researchers audited the EHR to determine if the messages were read.
- Outcomes were assessed through EHR data to determine when patients completed their WCC.
- The analysis of COVID-19 vaccinations was limited to patients 12 years old and older due to FDA approval at the time of the study.

**INTERVENTION (# IN THE GROUP):** 315

**COMPARISON (# IN THE GROUP):** 315

**FOLLOW-UP PERIOD:** Eight weeks

**RESULTS:**

Primary Outcome –

- There was greater completion of WCC within eight weeks in both intervention groups compared to control.
  - There were 76 WCC in the standard message group (24%; aRR 1.9; 95% CI, 1.4–2.6).
  - There were 61 WCC in the tailored message group (19%; aRR 1.5; 95% CI, 1.1–2.1).
  - There were 40 completed WCC in the control group (13%).

Secondary Outcome –

- COVID-19 vaccination rates were also higher in the intervention groups.
  - There were 14 in the standard group (17%; aRR 4.8; 95% CI, 1.4–15).
  - There were four in the tailored group (5%; aRR 1.5; 95% CI, 0.24–7.9).
  - There were three in the control group (4%).

**LIMITATIONS:**

- Study population (low income, predominantly Black) and drawn from academic health center settings, limits generalizability.
- Randomization led to study subjects living in the same household being assigned to intervention and control group arms, which exposed controls to messaging.

- Wide confidence intervals derived in the secondary outcome (rates of COVID-19 vaccination) depreciate the interpretation of messaging effects.

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# Smartphone-Based Lactation Counseling and its Effects on Lactation Rates

**Smartphone-Based Counseling and Support Platform and the Effect on Postpartum Lactation: A Randomized Controlled Trial**

Miremberg H, Yirmiya K, Rona S, et al. Smartphone-based counseling and support platform and the effect on postpartum lactation: a randomized controlled trial. *Am J Obstet Gynecol MFM*. 2022;4(2):100543. doi:10.1016/j.ajogmf.2021.100543



**KEY TAKEAWAY:** Smartphone-based daily feedback and counseling platform between postpartum patients and a multidisciplinary lactation support team increases lactation rates after delivery.

**STUDY DESIGN:** Randomized controlled trial, non-blinded

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Breastfeeding has many benefits for both the mother and baby. However, many women end up quitting sooner than they had initially planned. Interventions such as smartphone-based lactation counseling can potentially help increase lactation rates and duration.

**PATIENTS:** Women who planned to breastfeed for at least six months

**INTERVENTION:** Smartphone-based lactation counseling

**CONTROL:** Routine lactation counseling

**PRIMARY OUTCOME:** Lactation rates at three months after delivery

Secondary Outcome: Lactation rates at two weeks, six weeks, and six months after delivery plus patient satisfaction

**METHODS (BRIEF DESCRIPTION):**

- Women between 18–45 years old with singleton gestations delivered at full term who planned to breastfeed for six months and owned a smartphone.
- Patients were nonblinded and randomized to one of the following groups:
  - Group that received additional daily lactation counseling and support:
    - Patients had the app installed on their smartphone before discharge from the hospital. They could send any question or concern about lactation to the team in the app and get individualized responses via email within 24 hours. The patients could send questions regarding any emotional distress during this period. Patients who did not use the app for two weeks or more were contacted and offered support. The app was available for six months.
  - Group that received routine lactation counseling:
    - Patients were offered and encouraged to meet with postpartum nurses for lactation support at least once before discharge.
- Outcomes were measured by full or partial lactation rates at varying intervals.
  - Lactation was measured at two weeks, six weeks, three months, and six months.
  - Patient satisfaction was also measured.

**INTERVENTION (# IN THE GROUP):** 97

**COMPARISON (# IN THE GROUP):** 100

**FOLLOW-UP PERIOD:** Two weeks, six weeks, three months, and six months after delivery

**RESULTS:**

Primary Outcome –

- Patients randomized to the app group demonstrated a higher rate of lactation at three months after delivery (81.4% app vs 69% control, *P*=.049).

Secondary Outcome –

- Patients randomized to the app group demonstrated a higher rate of lactation at six weeks after delivery (96.9% app vs 82% control, *P*<.001).
- No difference in lactation rates were demonstrated between the app group and control group at two weeks (98.9% app vs 97% control, *P*=.621) and six months (59.8 % app vs 49% control, *P*=.775) after delivery.
- Patients in the app group reported excellent satisfaction from the use of the application.

**LIMITATIONS:**

- Virtual lactation support without hands-on help has not been extensively studied.
- The decision to stop breastfeeding sooner than planned is multifactorial and many of those factors could not be accounted for.

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# Effect of Daily Vitamin D3 Supplementation on Fracture Risk in Healthy U.S. Adults: A Randomized Controlled Trial

**Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults**

LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. *N Engl J Med*. 2022;387(4):299-309. doi:10.1056/NEJMoa2202106



**KEY TAKEAWAY:** Daily supplementation with 2000 IU of vitamin D3 did not significantly reduce the risk of total fractures, nonvertebral fractures, or hip fractures compared to placebo among generally healthy U.S. adults.

**STUDY DESIGN:** Multi-center, randomized controlled trial, double-blinded

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Fractures are a significant public health concern, particularly among older adults, with millions of osteoporotic fractures occurring annually. Osteoporosis and low bone mass affect many Americans, and vitamin D supplements are commonly recommended to promote bone health. Despite these recommendations, evidence regarding vitamin D's effectiveness in preventing fractures is inconclusive.

**PATIENTS:** Healthy adults (men 50 years old or older and women 55 years old or older)

**INTERVENTION:** Daily dose of 2000 IU of vitamin D3 (cholecalciferol) as a supplement

**CONTROL:** Placebo

**PRIMARY OUTCOME:** First incident of total fractures, nonvertebral fractures, and hip fractures

**METHODS (BRIEF DESCRIPTION):**

- Participant Selection: This is an ancillary study of the Vitamin D and Omega-3 Trial (VITAL), which included 25,871 people.
  - 12,786 U.S. men (age ≥50 years) and 13,085 women (age ≥55 years)
  - 5,106 Black participants from all 50 states
- Participants were generally healthy and were not selected based on vitamin D deficiency or fracture history.
  - The baseline vitamin D level was 30.7 on average.
- The trial included a run-in phase to collect baseline data with a three-month placebo and participant randomization.
- The primary endpoints were the first incident total, nonvertebral, and hip fractures.
  - Secondary endpoints included major osteoporotic, pelvic, and wrist fractures.
- Participants provided baseline and follow-up blood samples.
- Questionnaires collected information on demographics, medical history, medication use, supplement use, physical activity, falls, and fractures.
  - Incident fractures were reported by participants and verified through medical records.
- Statistical Analysis: Cox proportional-hazards models were used to estimate the hazard ratio for fracture incidence, adjusting for relevant factors.
  - Subgroup analyses were conducted to explore treatment effects in specific populations.

**INTERVENTION (# IN THE GROUP):** 12,972

**COMPARISON (# IN THE GROUP):** 12,944

**FOLLOW-UP PERIOD:** Median 5.3 years

**RESULTS:**

Primary Outcome –

- Risk of first incident total fractures: Vitamin D supplementation did not reduce the risk of complete fractures (hazard ratio 0.98; 95% CI, 0.89–1.1; odds ratio 0.97; 95% CI, 0.89–1.1).
- Risk of nonvertebral fractures: Vitamin D supplementation did not reduce the risk of nonvertebral fractures (hazard ratio 0.97; 95% CI, 0.87–1.1; odds ratio 0.96; 95% CI, 0.87–1.1).
- Risk of hip fractures: Vitamin D supplementation did not reduce the risk of hip fractures (hazard ratio: 1.0; 95% CI, 0.70–1.5; odds ratio 1.0; 95% CI, 0.69–1.5).
- There was no effect modification according to baseline age, sex, race or ethnic group, BMI, or personal use of supplemental calcium or vitamin D.

Secondary Outcome –

- Confirmed incident fractures excluding toe, finger, skull, periprosthetic, and pathologic fracture.

- Total fractures: Vitamin D supplementation did not reduce the risk of fractures (hazard ratio 0.99; 95% CI, 0.89–1.1).
- Risk of hip fractures: Vitamin D supplementation did not reduce the risk of hip fractures (hazard ratio of 1.0; 95% CI, 0.70–1.5).
- Risk of nonvertebral fractures: Vitamin D supplementation did not reduce the risk of nonvertebral fractures (hazard ratio of 0.97; 95% CI, 0.87–1.1).

**LIMITATIONS:**

- The study relied on self-reporting of supplement adherence, introducing potential inaccuracies and bias.
- The study did not account for influential factors like physical activity, diet, and concurrent medications.
- Limited statistical power in some subgroups affected the ability to detect differences in fracture risk.
- Specific patient populations, such as those with cancer, cardiovascular disease, or hypercalcemia, were excluded from the study.

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# Battle of the Clots: Apixaban vs. Warfarin for Mechanical Valve Recipients

**Apixaban or Warfarin in Patients with an On-X Mechanical Aortic Valve**

Wang T, Svensson L, Wen J, et al. Apixaban or warfarin in patients with an On-X mechanical aortic valve. *NEJM Evid.* 2023;2;(7). Published 2023 May 6. doi:10.1056/EVIDoa2300067



**KEY TAKEAWAY:** While the risk of a major bleeding event is lessened with apixaban use when compared to warfarin, apixaban is much less effective at preventing thromboembolic events in patients with an On-X mechanical aortic valve.

**STUDY DESIGN:** Prospective, randomized, open-label trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** The standard of care for anticoagulation in patients after the placement of a mechanical aortic valve is warfarin. The bleeding risk of warfarin therapy, along with other barriers to care such as INR monitoring, has encouraged the exploration of other direct oral anticoagulants (DOACs) for use in this population. A prior study of one DOAC, Dabigatran, showed significant inferiority in efficacy and safety when compared to warfarin. This study tested another DOAC, apixaban, against warfarin.

**PATIENTS:** Patients with On-X mechanical aortic valves

**INTERVENTION:** Apixaban 5 mg BID

**CONTROL:** Warfarin with target INR between 2.0–3.0

**PRIMARY OUTCOME:** Efficacy (Rate of thromboembolic events)

Secondary Outcome: Safety (Rate of major bleeding events)

**METHODS (BRIEF DESCRIPTION):**

- After controlling for demographics, use of daily aspirin, and length of time since valve placement, participants were randomly sorted into either an intervention group receiving apixaban 5 mg BID or a control group receiving warfarin to a target INR of 2.0–3.0.
- Patients could be transitioned to apixaban 2.5 mg BID if they met the dose reduction criteria at any point in the trial (n=2).
- Patient inclusion criteria included age >18 years old and placement of an On-X mechanical aortic valve more than three months prior to the study.
- Monthly follow-up for both groups resulted in the collection of 480 patient-years from the apixaban group and 467 patient-years from the warfarin group.
- Outcomes were measured by the rate of thromboembolic events (efficacy) and major bleeding events (safety) per patient year.
- A thrombotic event was defined as "Any thrombus, not caused by infection, attached to or near an implanted On-X valve that occluded part of the blood flow path, interfered with valve function, or was sufficiently large to warrant treatment other than continued anticoagulation," as adjudicated by a blinded clinical events committee.
- Medication labels were not blinded, so participants knew whether they were receiving apixaban or warfarin.
- Adverse events were adjudicated by blinded researchers who did not know which medication the patient had been on.
- Patients were required to also take aspirin 81 mg daily, or have a documented contraindication.

**INTERVENTION (# IN THE GROUP):** 433

**COMPARISON (# IN THE GROUP):** 430

**FOLLOW-UP PERIOD:** Approximately 13.5 months

**RESULTS:**

Primary Outcome –

- 20 thromboembolic events occurred in the apixaban group (4.2% per patient-year; 95% CI, 2.3–6.0).
- Six thromboembolic events occurred in the warfarin group (1.3% per patient-year; 95% CI, 0.3–2.3).
- Apixaban resulted in more thromboembolic events than warfarin; therefore, apixaban is less efficacious than warfarin (Between-group difference of 2.9% per patient-year; 95% CI, 0.8–5.0).
    - Noninferiority of apixaban was not concluded, as the upper limit of the difference between apixaban rates and warfarin rates (5.0%) was greater than 1.75%.

Secondary Outcome –

- Apixaban led to a similar number of major bleeding events compared to warfarin (3.6% per patient-year vs 4.5% per patient-year, respectively; HR 0.6; 95% CI, 0.3–1.3).

**LIMITATIONS:**

- Only the On-X brand of mechanical aortic valves were studied.
- 90% of participants identified as White.

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# COVID-19: A Risk Factor for Prematurity, Birthweight and Obstetric Complications

**Impact of SARS-CoV-2 Infection on Risk of Prematurity, Birthweight and Obstetric Complications: A Multivariate Analysis From a Nationwide, Population-Based Retrospective Cohort Study**

Simon E, Gouyon JB, Cottenet J, et al. Impact of SARS-CoV-2 infection on risk of prematurity, birthweight and obstetric complications: A multivariate analysis from a nationwide, population-based retrospective cohort study. *BJOG*. 2022;129(7):1084-1094. doi:10.1111/1471-0528.17135



**KEY TAKEAWAY:** Infection with SARS-CoV-2 in singleton pregnancies increases the risk of prematurity and is associated with obstetric complications such as hypertension, pre-eclampsia, diabetes, and cesarean delivery.

**STUDY DESIGN:** Nationwide population-based retrospective cohort study

**LEVEL OF EVIDENCE:** STEP 3

**BRIEF BACKGROUND INFORMATION:** Many publications and studies have investigated the impact of COVID-19 on maternal and perinatal outcomes with significant differences in different countries and income statuses. However, those studies focused on the overall impact of health measures rather than on complications. Prior studies lacked modeling to avoid confounding bias; few were national or regional studies. This study allows for comparing COVID-19 infection with other risk factors of prematurity. It displays the associations of infection, the importance of infection control, and the need for further research, including the benefits of lockdown precautions.

**PATIENTS:** Singleton births

**INTERVENTION:** Positive COVID-19 status during newborn's birth stay or mother's delivery stay

**CONTROL:** Negative COVID-19 status

**PRIMARY OUTCOME:** Incidence of premature deliveries, fetal macrosomia, and obstetrical complications

Secondary Outcome: Incidence of ICU admissions and non-COVID infections

**METHODS (BRIEF DESCRIPTION):**

- The Programme de Medicalisation des Systemes d'Information (PMSI) database was utilized to access records for all public and private hospital admissions in France.
- 510,387 singleton births were identified between March and December of 2020 and distinguished by the presence or absence of an ICD-10 code for COVID-19 diagnosis during a newborn's birth stay or mother's delivery stay.
- The World Health Organization's classification of prematurity, defined as before 37 weeks of gestation, was utilized.
    - Included were categories of extreme preterm (<28 weeks), moderate preterm (28–31 weeks), and later preterm (32–36 weeks) births.
- The mean maternal age was 31 years, and approximately 53% of the study population of women did not have a previous delivery within the past 10 years.
- Maternal comorbidities were obtained via ICD-10 and CCAM codes during the maternal delivery hospitalization or another hospitalization during pregnancy.
- Variables of neonatal sex, gestational age, birth weight, malformations, maternal age, mode of delivery, maternal comorbidities, and non-COVID infections were identified and compared.
- The prematurity risk and macrosomia risk were assessed via separate adjusted logistic regression of COVID-19 infection, neonatal sex, maternal age, maternal comorbidities, malformations, and lack of childbirth in the previous 10 years.
- Results were reported as frequency percentages, means +/-, standard deviations and medians, and odds ratios or adjusted odds ratios.
- Outcomes were reported as associations of COVID-19 with prematurity in two different gestational age groups (28-31 weeks and 32-36 weeks), fetal macrosomia, and obstetrical complications such as Hypertension, Pre-Eclampsia, Diabetes, and Cesarean Delivery.
    - Secondary outcomes were reported as the association of COVID-19 with ICU admissions and non-COVID infections and the risk of prematurity and macrosomia with COVID-19, obstetrical complications, and maternal/fetal demographics (maternal age, newborn gender).

**INTERVENTION (# IN THE GROUP):** 2,927

**COMPARISON (# IN THE GROUP):** 507,460

**FOLLOW-UP PERIOD:** Nine months

**RESULTS:**

Primary Outcome –

- COVID-19 was associated with increased prematurity, especially in the 28–31 and 32–36 gestational week groups, increased fetal macrosomia, and increased obstetrical complications of Hypertension, Pre-Eclampsia, Diabetes, and Cesarean Delivery.
  - Delivery via C-section (27% vs 20; $p<.01$)
  - Hypertension (6.4% vs 4.1%; $p<.01$)
  - Diabetes (19% vs 14%; $p<.01$)
    - Pre-existing (1.7% vs 0.8%; $p<.01$)
    - Gestational (17% vs 14%; $p<.01$)
  - Obesity (4.4% vs 2.7%; $p<.01$)
  - Non-COVID infections (24% vs 9.7%; $p<.01$)
  - ICU Admissions (2.7% vs 0.2%; $p<.01$)
  - Prematurity (9.8% vs 5.4%; $p<.01$)
    - 28-31 weeks (1.3% vs 0.6%; $p<.01$)
    - 32-36 weeks (7.7% vs 4.3%; $p<.01$)
- No significant difference was found between COVID-19 and non-COVID groups for association with no previous childbirth within 10 years, retroplacental hematoma comorbidity, hospital maternal death, male neonatal sex, prematurity within the 22–27 week gestation category, small for gestational age births, or malformations.

Secondary Outcome –

- COVID-19 was associated with more ICU admissions and more non-COVID infections, including chorioamnionitis and other infections related to preterm birth.
- Risk of Prematurity significantly associated with:
  - COVID-19 infection (aOR 1.8; 95% CI, 1.5–2.0)
  - Male sex (aOR 1.1; 95% CI, 1.1–1.2)
  - Maternal age ≤18 (aOR 1.7; 95% CI, 1.5–1.9)
  - Maternal age ≥40 (aOR 1.2; 95% CI, 1.1–1.3)
  - No childbirth within the previous 10yrs (aOR 1.2; 95% CI, 1.1–1.2)
  - Retroplacental hematoma (aOR 19; 95% CI, 17–21)
  - Hypertension (OR 5.6; 95% CI, 5.4–5.8])
  - Pre-Eclampsia (aOR 9.6; 95% CI, 9.2–10)
  - Hypertension (aOR 1.70; 95% CI, 1.6–1.8)
  - Obesity (aOR 1.2; 95% CI, 1.1–1.3)
  - Malformation (aOR 3.6; 95% CI, 3.5–3.8)
  - Diabetes (OR 1.3; 95% CI, 1.2–1.3)
    - Pre-existing (aOR 2.8; 95% CI, 2.5–3.1)
    - Gestational (aOR 1.1; 95% CI, 1.0–1.1)
- Risk of Macrosomia significantly associated with:
  - Male sex (aOR 2.4; 95% CI, 2.2–2.5)
  - Obesity (OR 2.5; 95% CI, 2.2–2.9)
  - Diabetes (OR 1.7; 95% CI, 1.6–1.8)
    - Pre-existing with obesity (aOR 3.3; 95% CI, 2.1–5.1)
    - Gestational with obesity (aOR 1.4; 95% CI, 1.0–1.8)
    - Pre-existing without obesity (aOR 6.1; 95% CI, 5.0–7.4)
    - Gestational without obesity (aOR 1.3; 95% CI, 1.2–1.5)

**LIMITATIONS:**

- Results from a hospital medical-administrative database were used, which can lack sufficiently reliable and explanatory data.
  - Also, results may not include certain variables such as diet, smoking, or gestational thromboembolic events.
- While some infections correlating with preterm birth were considered, identifying all infections during pregnancy was limited.
- Assessment of parity was limited to the previous 10 years.
- While gestational vs pre-existing diabetes were identified, information regarding glycemic control was unavailable.
- The study did not consider COVID during pregnancy or those not tested for COVID-19.
  - Positive status was only determined if the mother or newborn tested positive on PCR and was medically verified during the hospital stay.

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