GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of June 7 - 11, 2021

SPOTLIGHT: MAb Prevention of RSV in Preterm Infants

- The Effects of Periconceptional Diet on Maternal and Neonatal Outcomes
- Utility Beyond Erectile Dysfunction
- Getting Old Does Not Mean Being Fat & Lazy

MAb Prevention of RSV in Preterm Infants

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *N Engl J Med*. 2020 Jul 30; 383(5):415-425. doi: 10.1056/NEJMoa1913556. Erratum in: *N Engl J Med.* 2020 Aug 13; 383(7):698.

KEY TAKEAWAY: Compared to placebo, treatment with Nirsevimab resulted in a decreased incidence of Respiratory Syncytial Virus (RSV) - associated lower respiratory tract infections (LRTI).

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: RSV is the most common cause of LRTIs, and a leading cause of death among infants and young children. The standard of care is supportive management. Current RSV prophylaxis, RSV immunoglobulin G (Palivizumab), is administered in five monthly injections and is reserved for highest risk infants.

PATIENTS: Healthy preterm infants

INTERVENTION: Single dose 50 mg IM injection of Nirsevimab at the start of an RSV season (usually mid-September to mid-April).

CONTROL: Single dose IM injection normal saline placebo at the start of an RSV season.

OUTCOMES:

- Primary outcome: Incidence of RSV-associated LRTI.
- Secondary efficacy end point: Hospitalization for RSV-associated LRTI.

METHODS (BRIEF DESCRIPTION):

- Patients were excluded if they had acute illness, previously had RSV infection, or had already received RSV prophylaxis
- Patients were included if they were healthy preterm infants born 29 weeks 0 days to 34 weeks 6 days of gestation, whom were 1 year of age or younger, and entering their first full RSV season.
- Randomization of patients in 2:1 ratio to receive either a single IM injection of 50 mg Nirsevimab or IM normal saline during 2 month period before RSV season
- Patients were monitored for respiratory illnesses during 150 days post-injection and diagnosed with RSV-associated LRTI if the following criteria were present:
  - A positive RSV PCR testing performed at central laboratory
  - Exam revealed rhonchi, rales, crackles, or wheeze indicating lower respiratory tract involvement
  - One indication of clinical severity (tachypnea, hypoxemia, or clinical signs of respiratory distress)

INTERVENTION (# IN THE GROUP): 969

COMPARISON (# IN THE GROUP): 484

FOLLOW UP PERIOD: Bimonthly telephone visits and in-person visits on days 8, 31, 91, 151 and 361 after dose administration

RESULTS:

- 97.5% of combined randomized participants completed the 150-day efficacy period.
- Infants receiving Nirsevimab had lower risk of RSV-associated LRTIs (either inpatient or outpatient) compared to infants receiving placebo (2.6% vs 9.5%; Hazard Ratio [HR] 0.26; 95% CI, 0.16-0.43; NNT=14)
- Infants who received Nirsevimab had lower risk of hospitalization due to RSV infection compared to placebo (0.8% vs 4.1%; HR 0.19; 95% CI, 0.08-0.44; NNT=30)
- Infants receiving Nirsevimab also experienced lower hospitalizations from any respiratory illness (5.5% vs 9.5%; Relative Difference 43%; 95% CI, 16 to 61)
- Frequency of adverse events were similar in both groups.
  - No serious adverse events related to Nirsevimab including hypersensitivity or anaphylactic reactions were reported.

LIMITATIONS:

- Funded by AstraZeneca and Sanofi Pasteur.
- Restricted by participants' age and gestational age at birth.

- No direct comparison between Nirsevimab and other anti-RSV monoclonal antibodies and maternal vaccines.
- Study participation limited to N=1,447; larger study would be required to detect less-common adverse events.

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The Effects of Periconceptional Diet on Maternal and Neonatal Outcomes

Quality of periconceptional dietary intake and maternal and neonatal outcomes

Yee LM, Silver RM, Haas DM, et al. Quality of periconceptional dietary intake and maternal and neonatal outcomes. *Am J Obstet Gynecol*. 2020; 223(1):121.e1-121.e8. doi:10.1016/j.ajog.2020.01.042

KEY TAKEAWAY: Patients with lower Healthy Eating Index (HEI) scores during the periconceptional stage experienced greater adverse maternal and neonatal outcomes.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Reproductive age women in the United States have overall poor quality dietary intake. It is unknown whether periconceptional dietary quality is associated with maternal and neonatal outcomes.

PATIENTS: Nulliparous women between 6+0 weeks and 13+6 weeks

INTERVENTION: Modified Block 2005 Food Frequency Questionnaire

CONTROL: N/A

OUTCOMES: Differences between patient demographic and clinical characteristics by Health Eating Index (HEI) quartiles; maternal and neonatal outcomes by HEI quartiles

METHODS (BRIEF DESCRIPTION):

- Participants were 10,038 nulliparous women receiving obstetrical care at 8 United States centers
- Food frequency questionnaires were scored using the HEI.
- Outcomes recorded at least 30 days postpartum via records review.
- Outcomes assessed included: gestational diabetes mellitus, major perineal laceration, cesarean delivery, postpartum hemorrhage requiring transfusion, hypertensive disorders, preterm birth, admission to NICU, small-for-gestational-age infant, low birth weight, and macrosomia
- Potential confounders accounted by authors
- Chi-square, ANOVA, and logistic regression used to examine differences between demographics, clinical characteristics and between maternal/neonatal outcomes by HEI quartiles.

INTERVENTION (# IN THE GROUP): 10,038 (HEI data obtained from 8,259)

COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: 3 years

RESULTS:

Women in the lowest HEI quartile (poorest quality dietary intake) compared to the women in the higher HEI quartiles (best quality dietary intake):

- Postpartum hemorrhage requiring transfusion
  - HEI-Q1 aRR 3.3; 95% CI, 1.4–7.5
- Hypertensive disorder of pregnancy
  - HEI-Q1 aRR 1.1; 95% CI, 1.0–1.3
- Cesarean delivery
  - HEI-Q1 aRR 1.2; 95% CI, 0.8–1.6
- Preterm birth (<37 weeks)
  - HEI-Q1 aRR 1.2; 95% CI, 1.0–1.6
- NICU admission
  - HEI-Q1 aRR 1.2; 95% CI, 1.0–1.4
- Small-for-gestational age (<10th percentile)
  - HEI-Q1 aRR 1.2; 95% CI, 1.0–1.5
- Low birth weight (<2,500 g)
  - HEI-Q1 aRR 1.3; 95% CI, 1.0–1.7
- Major perineal lacerations
  - HEI-Q1 aRR 0.6; 95% CI, 0.4–0.9
- Macrosomia (>4,000 g)
  - HEI-Q1 aRR 0.6; 95% CI, 0.4–0.7
- Gestational diabetes
  - HEI-Q1 aRR 1.2; 95% CI, 0.8–1.6

LIMITATIONS:

- Results may be affected by unaccounted confounding variables.
- Self-reported data presents risk for recall bias.
- Recruitment from only large academically affiliated medical centers may limit generalizability.

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Utility beyond erectile dysfunction: The novel use of sildenafil citrate for intrapartum fetal compromise

Safety and efficacy of sildenafil citrate to reduce operative birth for intrapartum fetal compromise at term: a phase 2 randomized controlled trial

Turner J, Dunn L, Tarnow-Mordi W, Flatley C, Flenady V, Kumar S. Safety and efficacy of sildenafil citrate to reduce operative birth for intrapartum fetal compromise at term: a phase 2 randomized controlled trial. *Am J Obstet Gynecol*. 2020 May; 222(5):401–414.

KEY TAKEAWAY: Oral sildenafil citrate reduced the risk of cesarean section or operative vaginal delivery in cases of intrapartum fetal compromise by 51% compared to placebo.

STUDY DESIGN: Phase 2 RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Intrapartum fetal compromise and fetal distress from reduced uteroplacental blood flow and reduced placental function account for 27% of cesarean deliveries in the U.S. Sildenafil citrate increases uteroplacental and fetal blood flow. No previous studies have evaluated its use to improve uteroplacental blood flow during the intrapartum period to prevent fetal compromise during labor.

PATIENTS: Term pregnant women 18–50 years old

INTERVENTION: Sildenafil citrate 50mg orally every 8 hours, up to 150 mg

CONTROL: Placebo

OUTCOMES: Primary outcomes: Rates of operative birth, mean indices of fetal and uteroplacental perfusion
Secondary Outcomes: Composite indicators of fetal compromise (pathologic fetal heart rate abnormalities, meconium-stained amniotic fluid), need for intrapartum fetal blood sampling, concentration of sildenafil citrate in maternal and cord blood, adverse neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- Included patients had a single, structurally normal cephalic presenting fetus and planned term vaginal delivery at single hospital in Australia
- Participants meeting inclusion criteria allocated via computer-generated sequence.
- Labor managed uniformly for all participants.
- Ultrasound of fetal and uteroplacental perfusion before and 2–4 hours after initial dose of medication.
- Maternal and cord blood samples obtained to evaluate levels of sildenafil and N-desmethyl sildenafil.
- Fetal scalp blood samples to measure lactate when indicated.
- Triple blinded, assessed via intention-to-treat analysis.

INTERVENTION (# IN THE GROUP): 150 (intention-to-treat), 137 (per protocol)

COMPARISON (# IN THE GROUP): 150 (intention-to-treat), 131 (per protocol)

FOLLOW UP PERIOD: Through immediate postpartum and neonatal period

RESULTS:

Primary Outcomes:

- Sildenafil significantly reduced rate of operative birth for intrapartum fetal compromise compared to placebo (18% vs 37%; Relative Risk (RR) 0.49; 95% CI, 0.33–0.73; NNT 5).
- No statistically significant difference in mean indices of fetal and uteroplacental perfusion compared to placebo (all *P*>.05).

Secondary Outcomes:

- Sildenafil significantly reduced composite measures of fetal compromise compared to placebo (25% vs 45%; RR 0.57; 95% CI, 0.41–0.79; NNT 5).
- There was no difference between sildenafil and placebo groups in rates of intrapartum fetal scalp sampling (2% vs 6%; RR 0.30; 95% CI, 0.08–1.07).
- There was no difference in neonatal outcomes between sildenafil and placebo (20% vs 21%; RR 0.97; 95% CI, 0.62–1.5).
- No differences in maternal adverse events noted between groups.

LIMITATIONS:

- Limited power for fetal and uteroplacental perfusion data due to limited sonography
- Relatively small sample size, phase 2 trial, single site limits generalizability
- Numerous exclusion criteria excluded over 500 patients.

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Getting Old Does Not Mean Being Fat & Lazy

Exercise Patterns in Older Adults Instructed to Follow Moderate or High Intensity Exercise Protocol – The Generation 100 Study

Reitlo LS, Sandbakk SB, Viken H, Aspivik NP, Ingebrigtsen JE, et al. Exercise patterns in older adults instructed to follow moderate- or high-intensity exercise protocol - the generation 100 study. *BMC Geriatr*. 2018; 18(1):208.

KEY TAKEAWAY: Older adults in Norway assigned to moderate-intensity training vs high-intensity interval training demonstrated good adherence over one year with walking the most common exercise, outdoor the most common location, and group exercise preferred in women.

STUDY DESIGN: RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The general perception of older adults is that they are frail and unable to perform moderate to high intensity exercises. Little is known about the types of exercise preferred in older adults. This study evaluated exercise patterns in older adults in Norway assigned to moderate vs high-intensity exercise over 12 months.

PATIENTS: Adults age 70-77 years old

INTERVENTION: High Intensity Interval Training (HIIT)

CONTROL: Moderate Intensity Training (MCT)

OUTCOMES: Primary Outcome: Assessment of exercise patterns via

- self-reported logs;
- frequency via mean sessions per week;
- intensity via Borg Scale;
- duration stratified by minutes;
- type of exercise, location, social setting

Secondary Outcomes: Demographics and health characteristics via National Population Registry

METHODS (BRIEF DESCRIPTION):

- Intervention: Two exercise groups of moderate intensity training (MCT) and high intensity interval training (HIIT)
- Control: Non-exercise group
- Statistics: Pearson chi-square test to assess association between intensity, type, location, and social setting of exercise training group.

INTERVENTION (# IN THE GROUP): 787 (618 in final analysis)

COMPARISON (# IN THE GROUP): 780

FOLLOW UP PERIOD: 12 months

RESULTS:

- Both the MCT and HIIT groups completed 2.2 exercise sessions each week.
- For both MCT and HIIT groups, outdoors most common exercise location (68% and 59% respectively).
- HIIT group with larger portion of exercise sessions at a gym (21% vs 18%, *P*<.01) and sports facility (9.8% vs 7.6%, *P*<.01) compared to MCT group.
- Walking most common exercise in MCT and HIIT groups, but MCT with more walking sessions (54% vs 41%, *P*<.01).
- HIIT group with more cycling sessions (14% vs 9.8%, *P*<.01), more jogging sessions (6.5% vs 3.2%, *P*<.01), more combined endurance and resistance training (10% vs 7.5%, *P*<.01), and more swimming (2.6% vs 1.7%, *P*<.01) compared to the MCT group.
- Women with more sessions together with others than men (56% vs 44%, *P*<.01).

LIMITATIONS:

- Self-reported data
- Selection bias
- Recall bias

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