GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of November 20 - 24, 2023

SPOTLIGHT: Will Taking Doxycycline After Sex Reduce the Risk of STI?

Will Taking Doxycycline After Sex Reduce the Risk of STI?

Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections

Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. *N Engl J Med.* 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

KEY TAKEAWAY: Doxycycline postexposure prophylaxis lowers the combined incidence of gonorrhea, chlamydia, and syphilis by two-thirds compared to standard care, supporting its use among MSM with recent bacterial STIs.

STUDY DESIGN: Open-label randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Sexually transmitted infections (STIs) are a global public health concern that affects millions of people each year. The current approaches to the prevention of bacterial STIs include promoting safe sex practices, as well as the provision of vaccines. In addition to these prevention strategies, postexposure prophylaxis with antibiotics, such as azithromycin and doxycycline, have been used in some settings to prevent bacterial STIs in individuals who have been potentially exposed to an infected partner. However, there is limited research on the effectiveness of postexposure prophylaxis with antibiotics for preventing bacterial STIs, and its use is not widely recommended by current guidelines.

PATIENTS: Men who have sex with men (MSM) and transgender women with an STI in the past year

INTERVENTION: Doxycycline

CONTROL: Standard care

PRIMARY OUTCOME: Combined incidence of gonorrhea, chlamydia, syphilis

METHODS (BRIEF DESCRIPTION):

- Eligible participants: At least 18 years old, assigned male sex at birth with a history of condomless sex with a male partner in the past 12 months and diagnosed with HIV (PLWH), using HIV PrEP, or previous STI diagnosis.
    - Exclusion criteria: Tetracycline allergy, doxycycline drug interactions, or prolonged doxycycline use.
- An open-label study was used to assess overall intervention effectiveness, biological efficacy, and changes in sexual behavior.
- Participants were randomly assigned in a 2:1 ratio to two groups:
    - Doxy-PEP group (prophylactic doxycycline after STI exposure)
    - Standard-care group (without doxy-PEP)
- Doxycycline group participants received three bottles containing 200 mg doxycycline hyclate delayed-release tablets at enrollment. Tablets were taken quarterly based on usage and participant request, aligned with sexual frequency.
- The study included quarterly visits and additional interim visits as needed, spanning 12 months with quarterly adherence assessments, side effect tracking, and acceptability evaluations at six and 12 months.
- Quarterly testing of the pharynx, rectum, and urine was done to check for the presence of gonorrhea and chlamydia and blood tests were done to check for the presence of syphilis.
- Stool samples were collected to analyze tetracycline resistance genes.

INTERVENTION (# IN THE GROUP): 433

COMPARISON (# IN THE GROUP): 208

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- There was a significant decrease in STI incidence with doxycycline vs standard of care in the PrEP cohort (RR 0.34; 95% CI, 0.24–0.46).
    - NNT to prevent an STI in three months= 4.7
- There was a significant decrease in STI incidence with doxycycline vs standard of care in the PLWH cohort (RR 0.38; 95% CI, 0.24–0.60).
    - NNT to prevent an STI in three months= 5.3

LIMITATIONS:

- Measuring adherence to doxy-PEP (post-exposure prophylaxis) was challenging due to difficulties in accurately determining condomless sex and event-driven PEP use.
- The quarterly computer-assisted surveys used to record sexual activity and doxycycline use were

limited by reliance on participants' recall, which may not be entirely accurate.

- Tetracycline susceptibility results were available in only 17% of gonorrhea cases, primarily due to a lack of *Neisseria gonorrhoeae* culture obtained before treatment and lower cultivability from extragenital infections.
- The study had a low enrollment rate of transgender women (less than 5%), which restricts the generalizability of the findings to this population.
- The study was conducted in two West Coast cities, which means that acceptability, adherence, and STI rates may vary in other settings.

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Intermittent Fasting Unleashed: How it Compares to Traditional Diets in Weight Loss and Health

Effects of Intermittent Fasting in Humans Compared to Non-Intervention Diet and Caloric Restriction: A Meta-Analysis of Randomized Controlled Trials

Gu L, Fu R, Hong J, Ni H, Yu K, Lou H. Effects of Intermittent Fasting in Human Compared to a Non-intervention Diet and Caloric Restriction: A Meta-Analysis of Randomized Controlled Trials. *Front Nutr.* 2022;9:871682. Published 2022 May 2. doi:10.3389/fnut.2022.871682

KEY TAKEAWAY: Intermittent fasting (IF) significantly decreased weight, body mass index (BMI), waist circumference (WC), and cholesterol compared to the usual diet. However, there was no significant difference in biophysical or metabolic outcomes between IF and caloric restriction except for WC.

STUDY DESIGN: Meta-analysis of 43 randomized controlled trials (N=2,483)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to low quality of included studies and heterogeneity)

BRIEF BACKGROUND INFORMATION: The rise in global metabolic disorders and obesity has directed attention towards lifestyle interventions such as diet, exercise, and IF. Although some research suggests the superiority of IF over traditional calorie restriction (CR) for weight loss, there remains a need for further evaluation of the effects of different types of IF.

PATIENTS: Adults attempting to lose weight

INTERVENTION: Intermittent fasting

CONTROL: Usual diet or CR

PRIMARY OUTCOME: Weight, BMI, waist circumference, cholesterol, fasting glucose, triglycerides

METHODS (BRIEF DESCRIPTION):

- Two independent researchers searched databases including PubMed, Web of Science, Cochrane Library, and Embase identified literature on IF through June 2021, using keywords specific to randomized trials and fasting methods.
- Individual study inclusion criteria were highly variable and were not always specified, but in general, participants were adults with BMI >25–30.
- Inclusion criteria: Human subjects involved in RCTs using various IF interventions including alternate-day fasting, time-restricted feeding, intermittent energy restriction, or Ramadan fasting.
- Control groups were usual diet ("non-intervention") which was not specifically defined, or CR. CR varied significantly by study, including Mediterranean diet, DASH diet, or continuous energy restriction.
- Two independent investigators assessed the quality of the screened RCTs using the Cochrane Collaboration tool, with disputes resolved by a third researcher.
- Outcomes including weight, BMI, WC, fasting glucose, and total cholesterol were extracted from the studies.
- Meta-analysis was done by calculating the weighted mean difference (WMD) between IF and control or CR for outcomes including weight, BMI, and waist circumference. Standardized mean difference (SMD) was calculated for cholesterol and triglycerides. A fixed-effect model was used for meta-analysis if heterogeneity (I^2) was <50%; otherwise, a random effects model was used.
- Comparisons were made between IF and usual diet (25 studies), or IF and CR (20 studies).

INTERVENTION (# IN THE GROUP): 1,277

COMPARISON (# IN THE GROUP): 1,206

FOLLOW-UP PERIOD: Variable; minimum one month with a median of three months

RESULTS:

Primary Outcome –

- IF led to a larger reduction in the following compared to the usual diet:
  - Weight (19 studies; WMD 1.1; 95% CI, 0.09–2.1)
  - BMI (WMD 0.38; 95% CI, 0.08–0.68)
  - WC (WMD 1.0; 95% CI, 0.06–2.0)
- IF was also associated with reductions in the following compared to usual diet:
  - Cholesterol (18 studies; SMD 0.13; 95% CI, 0.00–0.26)
  - Triglycerides (SMD 0.22; 95% CI, 0.09–0.35)
- There was no significant difference in fasting glucose between IF and the usual diet (16 studies; SMD 0.00; 95% CI, –0.14 to –0.13).

- There was no significant difference in outcomes between IF and CR except for a reduction in WC (10 studies; WMD 2.3; 95% CI, 0.57–4.0).

LIMITATIONS:

- Significant heterogeneity in the type of IF interventions, comparison groups (usual diet), and the study populations included.
- Low quality and high risk of bias of many included studies, as assessed using the Cochrane collaboration tool.
- Small effect size
- Lack of long-term follow-up

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Does Neprilysin Inhibition Offer Benefit in Treating Pre-HFpEF?

Effect of Sacubitril/Valsartan vs Valsartan on Left Atrial Volume in Patients with Pre-Heart Failure with Preserved Ejection Fraction: The PARABLE Randomized Clinical Trial

Ledwidge M, Dodd JD, Ryan F, et al. Effect of Sacubitril/Valsartan vs Valsartan on Left Atrial Volume in Patients with Pre-Heart Failure with Preserved Ejection Fraction: The PARABLE Randomized Clinical Trial. *JAMA Cardiol.* 2023;8(4):366-375. doi:10.1001/jamacardio.2023.0065

KEY TAKEAWAY: Among patients with pre-heart failure with preserved ejection fraction (pre-HFpEF) who have hypertension or diabetes, the addition of a neprilysin inhibitor (sacubitril) to valsartan demonstrated an unexpected increase in left atrial volume index (LAVI) along with improvement in markers of cardiovascular risk. Further investigation is needed to understand the risks and benefits of neprilysin inhibition in pre-HFpEF.

STUDY DESIGN: Single-center, double-blind, double-dummy, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The prevalence of pre-HFpEF is estimated to be 30–63% among older adults with diabetes or hypertension. Pre-HFpEF can be defined as the absence of heart failure symptoms with preserved ejection fraction but with structural heart abnormalities and elevated biomarkers of dysfunction. Prior studies have evaluated screening tools and interventions to prevent the progression of pre-HF and reduce the risk of cardiovascular events, but have lacked investigation into specific pharmacological treatments. No study to date has examined treating pre-HFpEF with sacubitril/valsartan.

PATIENTS: Adults with pre-HFpEF who have hypertension and/or diabetes

INTERVENTION: Sacubitril/valsartan (neprilysin inhibition)

CONTROL: Valsartan only

PRIMARY OUTCOME: Left atrial volume index (LAVI)
Secondary Outcome: Cardiovascular risk factors (LAVI, pulse pressure, N-terminal pro-BNP, time to first major cardiovascular event)

METHODS (BRIEF DESCRIPTION):

- The study was comprised of patients 40 years old and older with hypertension or diabetes who had an elevated BNP (20–280 pg/mL) or N-terminal pro-BNP (100–1,000 pg/mL)
  - Median age of 72 years old
  - 98% had hypertension
  - 24% had diabetes
- The intervention group received sacubitril/valsartan 49/51 mg orally twice daily, titrated to 97/103 mg twice daily after two weeks, along with a valsartan dummy (placebo), for a total of 18 months.
- The control group received valsartan 80 mg orally twice daily, titrated up to 160 mg twice daily after two weeks, along with a sacubitril/valsartan dummy, for a total of 18 months.
- Primary and secondary outcomes were adjusted for the following variables: Age, sex, diabetes, hypertension, obesity, and vascular disease.
- One of the measured outcomes in this study was LAVI, a predictor of left ventricular filling pressure and function.
  - Increased LAVI is associated with deterioration of cardiac function.
- Volumetric cardiac MRI was used to measure LAVI (in mL/m^2) as well as indicators of cardiovascular risk (changes in left ventricular end-diastolic volume index, N-terminal pro-BNP, pulse pressure, and time to the first major adverse cardiovascular event at baseline and at 18 months).
  - LAVI was indexed to body surface area using the DuBois formula.
- Patients were confirmed to have asymptomatic HFpEF (or pre-HFpEF) by experienced cardiology providers.
  - An H2FpEF score was used in this assessment.
  - Elevated H2FpEF scores are associated with symptomatic heart failure.

INTERVENTION (# IN THE GROUP): 122

COMPARISON (# IN THE GROUP): 128

FOLLOW-UP PERIOD: 18 months

RESULTS:

Primary Outcome –

- Sacubitril/valsartan resulted in a greater LAVI than valsartan alone (6.9 mL/m^2 vs 0.7 mL/m^2, respectively; *P*<.001).

Secondary Outcome –

- Left ventricular end-diastolic volume index was greater with sacubitril/valsartan than valsartan alone (7.1 mL/m^2 vs 1.4 mL/m^2, respectively; *P*=.02).
- Ambulatory pulse pressure was decreased more with sacubitril/valsartan than with valsartan alone (–4.2 mmHg vs –1.2 mmHg, respectively; *P*<.001).
- N-terminal pro-BNP was decreased more with sacubitril/valsartan than with valsartan alone (–18% vs +9.4%, respectively; *P*<.001).
- Time to the first major adverse cardiovascular event showed decreased risk in the intervention group (adjusted hazard ratio 0.38; 95% CI, 0.17–0.89).

LIMITATIONS:

- The study only included patients from a single outpatient cardiology center in Dublin of a largely homogenous European ancestry, making it difficult to generalize to other populations.
- There was some difficulty in defining HFpEF and 34 patients were noted to have a high H2FpEF score, suggesting a higher likelihood of symptomatic heart failure, without further functional assessments being done.
- The follow-up time of the study was limited to only 18 months and was impacted by the COVID-19 pandemic.

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Elementary School-Based Gardening Program May Benefit High Risk Youth from a Metabolic Standpoint

Effects of a School-Based Nutrition, Gardening, and Cooking Intervention on Metabolic Parameters in High-Risk Youth: A Secondary Analysis of a Cluster Randomized Clinical Trial

Davis JN, Landry MJ, Vandyousefi S, et al. Effects of a School-Based Nutrition, Gardening, and Cooking Intervention on Metabolic Parameters in High-risk Youth: A Secondary Analysis of a Cluster Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(1):e2250375. Published 2023 Jan 3. doi:10.1001/jamanetworkopen.2022.50375

KEY TAKEAWAY: School-based gardening programs may improve metabolic outcomes in elementary-aged children.

STUDY DESIGN: Cluster random control trial (RTC)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pediatric obesity is a growing public health issue across the United States. The role of a healthy diet is considered a crucial tool to address this issue. Previous studies have shown that exposure to nutrition and gardening education improves fruit and vegetable intake in school-aged children. The aim of this study is to examine the metabolic differences in students participating in school-based gardening, nutrition, and cooking interventions.

PATIENTS: Elementary schools

INTERVENTION: Texas Sprout program

CONTROL: Delaying intervention

PRIMARY OUTCOME: Metabolic markers including glucose, lipid, insulin levels, insulin resistance

METHODS (BRIEF DESCRIPTION):

- This study was conducted over a three-year period (2016–2019) and was implemented in three waves during nine months of school enrollment every year.
- 16 elementary schools were randomized into either intervention or control (delayed intervention).
- Schools met the following inclusion criteria: Majority Hispanic population (>50%), majority of children participated in lunch assistance program (representing a low-income population), within 60 miles of Austin, Texas, and no existing garden or gardening program.
- Study participants included 3rd–5th grade students and their parents who were notified at back-to-school events, home fliers, and classroom announcements. Children and parents provided written informed consent to participate.
- Texas Sprout program intervention:
  - Gardens were built at every intervention school.
  - Trained nutrition and garden educators taught a total of 18 one-hour lessons throughout the year as part of the normal school day. Every lesson included either a garden taste test or a cooking activity.
  - Educators also taught monthly 60-minute lessons to the parents (nine total sessions).
  - Control schools received the delayed intervention, identical to intervention schools, the following year.
- The control group received delayed intervention where they were treated with an identical intervention after the initial phase of the study.
- Child and parent baseline and postintervention data was collected at the beginning (within the first month of the academic year) and end of the school year (within the last month of the academic year). This included age, grade, sex, race, ethnicity, height, and weight.
- Fasting blood studies were conducted over one week at each school (prior to the start of school or on Saturday) and corresponded with the baseline and postintervention data time periods.
- Blood studies included fasting glucose, hemoglobin A1C, insulin levels, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.
- Insulin resistance was calculated vis homeostatic model assessment (fasting glucose times fasting insulin/22.5).
- These were optional. Children received a $20 incentive to participate while parents received free diabetes screening.

INTERVENTION (# IN THE GROUP): 1,053

COMPARISON (# IN THE GROUP): 1,006

FOLLOW-UP PERIOD: Three years

RESULTS:

Primary Outcome –

- Compared with the delayed intervention schools, students enrolled in the Texas Sprouts program had:

- 0.02% reduction in mean hemoglobin A1C (95% CI, 0.03%–0.14%)
- 6.4 mg/dL reduction in mean LDL cholesterol (95% CI, 3.8–9.0 mg/dL).

- No intervention effect was observed on fasting glucose, insulin level, insulin resistance, and lipid markers other than LDL as mentioned.

LIMITATIONS:

- The study represented a high-risk group and thus cannot be generalized to other pediatric populations.
- The sample size was too small to detect effect size.
- The study was only nine months long, and no follow-up postintervention data was collected (long-term outcomes).
- HbA1c was added as a measurement after the study began, resulting in less data than other metabolic markers.
- No intervention effects were noted outside of changes in A1C and LDL. This could be attributed to the fact that blood samples were collected at a single time point. Glucose and insulin levels fluctuate, and single time point blood draws may not be representative of that child's usual blood glucose response. More accurate tests are available (glucose tolerance testing, etc.) but are expensive and time-consuming.

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Is Postoperative Delirium Associated with Increased Rate of Cognitive Decline?

Six-Year Cognitive Trajectory in Older Adults Following Major Surgery and Delirium

Kunicki ZJ, Ngo LH, Marcantonio ER, et al. Six-Year Cognitive Trajectory in Older Adults Following Major Surgery and Delirium. *JAMA Intern Med*. 2023;183(5):442-450. doi:10.1001/jamainternmed.2023.0144

KEY TAKEAWAY: Experiencing delirium after major surgery is associated with an increased rate of cognitive decline.

STUDY DESIGN: Prospective, observational cohort study with long-term follow-up

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Delirium is a serious postoperative complication with increasing concerns about its association with long-term cognitive decline.

PATIENTS: >70 years old without dementia undergoing major elective surgery

INTERVENTION: Development of delirium after major surgery

CONTROL: No delirium postoperatively

PRIMARY OUTCOME: Dementia and rate of cognitive decline

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: Patients greater than 70 years old, English speaking, and elective surgery with an expected hospital stay of three days or greater.
- Exclusion criteria: Dementia, delirium or hospitalization within three months, terminal condition, severe blindness, deafness, schizophrenia, or alcohol abuse.
- Screening for dementia was performed after reviewing of medical records, Modified Mini-Mental State (3MS), and neuropsychological testing.
- Cognitive testing was performed preoperatively and multiple times postoperatively (1, 2, 6, 12, 18, 24, 30, 36, 48, 60, and 72 months) within 72 months of the postoperative period using 11 neuropsychological tests.
- A compositive measure of performance was assessed using the general cognitive performance (GCP) which was comprised of 11 neuropsychological tests including tests of attention, memory, language, and executive functioning.
- Variables of age, sex, racial and ethnic minority groups, education, medical co-morbidity, depression, cognitive impairment, presence of IADL impairment, and surgery type were controlled for and chosen as potential confounders as they were likely to be associated with delirium and long-term cognitive decline.

INTERVENTION (# IN THE GROUP): 134

COMPARISON (# IN THE GROUP): 426

FOLLOW-UP PERIOD: Six years

RESULTS:

Primary Outcome –

- 134 participants (24%) of the 560 participants developed postoperative delirium.
- Delirium was associated with an average 40% (95% CI, 64%–8%) annual increased rate of cognitive decline within 72 months following major surgery.
- Patients who experienced delirium were significantly more likely to die during the study follow-up (HR 1.4; 95% CI, 1.1–1.8).

LIMITATIONS:

- The study is observational so it cannot be determined if delirium directly causes cognitive decline or if persons with preclinical brain disease are more likely to develop delirium.
- The baseline cognitive function was not the same between the groups. The group that experienced delirium had lower 3MS scores (mean 91.6) and lower GCP scores (mean 54.7) at baseline than the no delirium group (mean 58.5).
- The study participants were predominantly White and highly educated, limiting generalizability.
- Post-delirium illness or medications were not controlled which may be related to the development of long-term cognitive decline.

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Buprenorphine Improves Neonatal Outcomes for Women Treated for Opioid Use Disorder During Pregnancy

Buprenorphine vs Methadone for Opioid Use Disorder in Pregnancy

Suarez EA, Huybrechts KF, Straub L, et al. Buprenorphine versus Methadone for Opioid Use Disorder in Pregnancy. *N Engl J Med.* 2022;387(22):2033-2044. doi:10.1056/NEJMoa2203318

KEY TAKEAWAY: Buprenorphine taken for opioid use disorder during pregnancy was associated with a lower risk of adverse neonatal outcomes compared to methadone use. However similar rates of adverse maternal outcomes were seen with buprenorphine when compared to methadone.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Opioid use disorder during pregnancy has steadily been increasing with the primary treatment being either buprenorphine or methadone. Previous studies have shown that buprenorphine was associated with fewer adverse outcomes. However, there were several limitations that may have affected the results. These studies also had limited information about maternal outcomes. This study aimed to examine the outcomes of buprenorphine vs methadone in a large US cohort that aimed to achieve careful control of confounding elements.

PATIENTS: Pregnant women and their newborns with opioid use disorder

INTERVENTION: Buprenorphine exposure during pregnancy

CONTROL: Methadone exposure during pregnancy

PRIMARY OUTCOME: Neonatal abstinence syndrome, preterm birth, small size for gestational age, low birth weight

Secondary Outcome: Maternal outcomes including cesarean section or severe complications such as a composite of potentially life-threatening conditions caused or aggravated by pregnancy

METHODS (BRIEF DESCRIPTION):

- Pregnant women 12–55 years old who had Medicaid coverage three months prior to the date of their last menstrual period to one month postpartum and infants who had Medicaid coverage through three months of age were included in this study.
- Women who received the opposite medication than the one they were assigned to were excluded.
- Infants with chromosomal abnormalities or exposure to a known teratogen were excluded.
- Exposure in infants with neonatal abstinence syndrome was defined as receiving the medication 30 days prior to delivery.
- For all other outcomes, exposure was defined as either occurring in early pregnancy (through week 19) or occurring in late pregnancy (after 20 weeks).
- Outcomes were determined at birth or within 30 days of birth.

INTERVENTION (# IN THE GROUP): 10,704

COMPARISON (# IN THE GROUP): 4,387

FOLLOW-UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- Neonatal abstinence syndrome was seen in 69% of infants exposed to methadone and 52% exposed to buprenorphine (adjusted relative risk [ARR] 0.79; 95% CI, 0.71–0.75).
- An inverse relationship was seen between buprenorphine and preterm birth regardless of exposure during early or late pregnancy when compared to methadone:
  - Early (ARR 0.58; 95% CI, 0.53–0.62)
  - Late (ARR 0.57; 95% CI, 0.53–0.62)
- An inverse relationship was seen between buprenorphine and small for gestational age when compared to methadone:
  - Early (ARR 0.72; 95% CI, 0.66–0.80)
  - Late (ARR 0.75; 95% CI, 0.69–0.82)
- An inverse relationship was seen between buprenorphine and low birth weight when compared to methadone:
  - Early (ARR 0.56; 95% CI, 0.50–0.63)
  - Late (ARR 0.56; 95% CI, 0.50–0.62)

Secondary Outcome –

- Risks of maternal adverse outcomes were similar in those who received methadone vs buprenorphine.

LIMITATIONS:

- The study authors did not have information on lifestyle and behavioral factors.
- The cohort was restricted to live births only.

- Inclusion required payment through Medicaid therefore patients with private insurance were not included.
- Dosage information for both buprenorphine and methadone were not known.

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Metformin in Pregnancy: Safe in the Long Term for Neonates

Metformin in Pregnancy and Risk of Adverse Long-Term Outcomes: A Register-Based Cohort Study

Brand KMG, Saarelainen L, Sonajalg J, et al. Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study. *BMJ Open Diabetes Res Care.* 2022;10(1):e002363. doi:10.1136/bmjdrc-2021-002363

KEY TAKEAWAY: Metformin and metformin + insulin used to treat gestational diabetes (GDM), polycystic ovary syndrome (PCOS), and type 2 diabetes mellitus (T2DM) prenatally are not associated with long-term complications in children, including obesity, hyperglycemia, hypoglycemia, or diabetes mellitus compared to insulin alone.

STUDY DESIGN: Retrospective nonrandomized controlled cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Currently, there is no approved indication for metformin use in pregnancy; however, its use is increasing for the treatment of GDM. Metformin is safe in pregnancy, with some studies showing a decreased risk of being large for gestational age (LGA) and hypoglycemia at birth compared to insulin. However, data examining long-term effects consists of random control trials that do not differentiate metformin use alone from metformin + insulin exposure in utero.

PATIENTS: Newborns born between 2004–2016

INTERVENTION: Maternal exposure to metformin or metformin + insulin

CONTROL: Maternal exposure to insulin alone

PRIMARY OUTCOME: Incidence of obesity, hypoglycemia, diabetes, hypertension, PCOS, changes in motor-social development

Secondary Outcome: Adverse conditions at birth, such as small for gestational age (SGA), LGA, preterm birth, neonatal mortality, hypoglycemia, hyperglycemia

METHODS (BRIEF DESCRIPTION):

- A register-based cohort study in Finland with singleton children born to women 18–45 years old treated with metformin and/or insulin for GDM, T2DM, or PCOS from 2004–2016 during pregnancy.
- Exclusion criteria were maternal diagnosis of type 1 diabetes mellitus, systemic glucocorticoids, or other antidiabetic medication during pregnancy.
- Groups included: Metformin, insulin, or metformin + insulin exposure.
- Children were followed from one week of age to death, with emigration at the end of the study period in 2016 (age 12 for oldest children).
- Incidence rates were reported per 1,000 patient-years with 95% CI.
    - Odds ratios with 95% CI were reported with adverse outcomes at birth for each group.
    - Hazard ratios with 95% CI were reported for primary outcomes for metformin and metformin + insulin compared to insulin alone.

INTERVENTION (# IN THE GROUP):

- Metformin only: 3,967
- Metformin + insulin: 889

COMPARISON (# IN THE GROUP): 5,273

FOLLOW-UP PERIOD: 12 years

RESULTS:

Primary Outcome –

- Metformin compared to insulin was not statistically different for long-term effects:
    - Rates of obesity (HR 1.1; 95% CI, 0.83–1.6)
    - Diabetes (HR 1.2; 95% CI, 0.51–2.8)
    - Hypoglycemia (HR 1.00; 95% CI, 0.61–1.6),
    - Hyperglycemia (HR 1.2; 95% CI, 0.63–2.4)
    - Challenges in motor-social development (HR 1.09; 95% CI, 0.93–1.34)
- Metformin + insulin compared to insulin was not statistically different for long-term effects:
    - Rates of obesity (HR 1.09; 95% CI, 0.76–1.6)
    - Hypoglycemia (HR 1.14; 95% CI, 0.71–1.8)
    - Hyperglycemia (HR 0.22; 95% CI, 0.05–1.01)
    - Diabetes mellitus (HR 0.14; 95% CI, 0.02–1.12)
    - Challenges in motor-social development (HR 1.11; 95% CI, 0.77–1.59)
- Metformin alone showed an increased risk of SGA (OR 1.6; 95% CI, 1.2–2.3), decreased risk of LGA (OR 0.8; 95% CI, 0.67–0.99), and neonatal hypoglycemia (OR 0.80; 95% CI, 0.72–0.89) compared to insulin alone at birth.

- Metformin + insulin showed an increased risk of LGA (OR 1.6; 95% CI, 1.2–2.05), preterm birth (OR 1.5; 95% CI, 1.10–1.9), and neonatal hypoglycemia (OR 1.3; 95% CI, 1.09–1.5) compared to insulin alone at birth.

LIMITATIONS:

- The study did not control for social factors (resource availability/access to care, socioeconomic status, diet/access to healthy food options).
- Median follow-up time was relatively short at 3.5 years.
- Maternal disease severity was not accounted for.

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