Medic Center

MEDICAL NEWS

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Maternal Infection in Pregnancy Ups Risk for Childhood Leukemia?

Liam Davenport

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Children born to mothers who had urinary or genital tract infections during pregnancy appear to have an increased risk for childhood leukemia, say researchers reporting a Danish registry analysis that may point to preventive strategies for the disease.

The research was published online today in *JAMA Network Open*.

- The team studied more than 2.2 million children born in Denmark over more than three decades, linking their records across multiple national registries to examine both later cancer risk and maternal infection rates.
- They found that, overall, at least one maternal infection during pregnancy was associated with a 35% increased risk for leukemia in the children, rising to 65% for urinary tract infections, and 142% for genital infections.
- "The findings of this large population-based cohort study suggest that maternal urinary and genital tract infections during pregnancy are associated with a higher risk of childhood leukemia in offspring," said lead author Jian-Rong He, DPhil, Division of Birth Cohort Study, Guangzhou Women and Children's Medical Center, Guangzhou, China.
- However, he added that "the associated absolute risk remained small given the rarity" of the disease. In absolute terms, the risk difference between exposed and unexposed children was 1.8 cases per 100,000 person-years for any infection, 3.4 cases per 100,000 person-years for urinary traction infection, and 7.1 cases per 100,000 person-years for genital tract infection.
- **Maternal infections during pregnancy may be associated with chromosomal and immunologic alterations in the fetus, the authors speculate**.
- "Given that little is known about the etiology of childhood leukemia," these results "suggest an important direction for research on the etiology of childhood leukemia as well as development of potential preventive measures," they write.

- In many countries, pregnant women are tested for urinary tract infection and bacterial vaginosis, and treated with antibiotics in antenatal care, as these infections are linked to adverse perinatal outcomes, they pointed out.

Study Details

- The team conducted a large population-based study that included all live births in Denmark between 1978 and 2015.
- After exclusions, they gathered information on 2,222,797 children, linking data from several national registries, including the Danish Medical Birth Register, the
- Danish National Patient Registry, and the Danish National Cancer Registry, to identify cases of childhood cancers and maternal infection during pregnancy.
- The results were then validated by comparing them with those in 2.6 million live births in Sweden between 1988 and 2014, for whom similar data was available through linkage with several Swedish registries.
- The Danish cohort were followed up for a mean of 12 years per person, yielding a total of 27 million person-years. Just over half (51.3%) were boys.
- **Cancer was diagnosed in 4362 children before 15 years of age**, of whom 1307 had leukemia (1050 had acute lymphocytic leukemia), 1267 had a brain tumor, 224 had lymphoma, and 1564 had other cancers.

- At least one infection during pregnancy was diagnosed in 81,717 mothers (3.7%). Urinary tract infections were the most common (in 1.7% of women), followed by genital tract infection (in 0.7%), digestive system infection (in 0.5%), and respiratory tract infection (in 0.3%).
- Women with any infection during pregnancy were more likely to be younger and primiparous than women who did not have infections, and they were also more likely to have fewer years of education, higher pre-pregnancy BMI, diabetes, and to smoke during early pregnancy.
- Preterm delivery and low-birth-weight infants were also more common in women with infections during pregnancy.
- Cox proportional hazards regression models revealed that, after adjustment for confounders, any maternal infection was associated with a hazard ratio of childhood leukemia of 1.35.
- Further analysis revealed that the association was driven by genital tract infection, at a hazard ratio for childhood leukemia of 2.42, and urinary tract infection, at a hazard ratio 1.65.
- Moreover, children born to women who had a sexually transmitted infection during pregnancy had a hazard ratio for developing leukemia of 3.13 compared with unexposed children.

- **There were no associations between other maternal infections and childhood leukemia.**
- The patterns of association between maternal infections and childhood leukemia were similar when looking at disease subtypes, as well as in the Swedish validation cohort, they add.
- When interpreting the results, the researchers caution that, as data on maternal infection were drawn from hospital data, "milder infections and those not diagnosed or treated in specialized health care facilities were not captured."
- "Also, some infections could be captured because the mother sought care for other, more serious conditions, which might bias the association of maternal infections and childhood leukemia."

Atorvastatin Cut Anthracycline Cardiac Dysfunction in Lymphoma: STOP-CA

Mitchel L. Zoler, PhD
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- NEW ORLEANS – Atorvastatin treatment of patients with lymphoma undergoing treatment with an anthracycline significantly cut the incidence of incident cardiac dysfunction by about two-thirds during 12 months of treatment, in a multicenter, randomized trial with 300 enrolled patients.
- "These data support the use of atorvastatin among patients with lymphoma being treated with anthracyclines where prevention of cardiac systolic dysfunction is important," concluded Tomas G. Neilan, MD, at the joint scientific sessions of the American College of Cardiology and the World Heart Federation. He highlighted that an important difference between the new study, STOP-CA, and a major prior study with a neutral effect published in 2022, was that STOP-CA "was powered for a major change" in cardiac function as the study's primary outcome, a decline from baseline in left ventricular ejection fraction (LVEF) of at least 10% that also reduced ejection fraction to less than 55%.
- "We can consider these medications [atorvastatin] for patients at higher risk for cardiac toxicity from anthracyclines, such as patients who receive a higher dose of an anthracycline, older patients, people with obesity, and women, commented Anita Deswal, MD, professor and chair of the department of cardiology at the University of Texas MD Anderson Cancer Center, Houston, who was not involved with the study.

STOP-CA: Statins To Prevent the Cardiotoxicity from Anthracyclines

- A basis for an 'important discussion' with patients
- "For patients receiving higher doses of anthracyclines, the STOP-CA trial says that whether to start a statin for cardiac protection is now an important discussion" for these patients to have with their treating clinicians. "That was not the case before today," commented Ronald M. Witteles, MD, a cardiologist and professor who specializes in cardio-oncology at Stanford (Calif.) University.
- "For a patient being treated for lymphoma or for another cancer and treated with equal or higher anthracycline doses, such as patients with a sarcoma, this trial's results at the very least warrant a discussion between physicians and patients to make the decision," Dr. Witteles, who was not involved in the study, said in an interview. But he also cautioned that "whether an individual patient should take a statin in this scenario is still not a no-brainer. While the trial was positive, it was for an imaging rather than for a clinical endpoint."
- Experts noted that a similar study with the clinical endpoint of heart failure would require both many more randomized patients as well as much longer follow-up. STOP-CA was not powered for this endpoint. During its 12-month duration, a total of 11 patients developed heart failure, with no between group difference.
- STOP-CA enrolled adults with lymphoma (Hodgkin or non-Hodgkin) and scheduled to undergo anthracycline treatment at eight U.S. centers and one in Canada, and excluded patients already on statin treatment or those for whom a statin was already indicated. Of the 300 enrolled patients, 286 had 12-month follow-up. Randomization assigned patients to receive either 40 mg daily of atorvastatin or placebo.

- Their cumulative, median anthracycline dose was 300 mg/m^2, which is typical for treating lymphoma, but higher than the typical dose use for patients with breast cancer. At baseline, average LVEF was 63%, and after 12 months this had declined to 59%. Forty-six of the 286 patients assessed after 12 months fulfilled the primary outcome of at least a 10–percentage point reduction from baseline in their LVEF and a decline in LVEF to less than 55%. Researchers used cardiac MR to assess LVEF at baseline, and in most patients at follow-up, but a minority of patients had their follow-up assessments by echocardiography because of logistical issues. Greater than 90% of patients were adherent to their assigned regimen.
- Tripled incidence of cardiac dysfunction in placebo patients
- The incidence of this outcome was 9% among the patients who received atorvastatin, and 22% among those on placebo, a significant difference. The calculated odds of the primary outcome was 2.9-fold more likely among the patients treated with placebo, compared with those who received atorvastatin, also a significant difference.
- The study's secondary outcome was patients who had at least a 5% drop from baseline in their LVEF and with a LVEF of less than 55% after 12 months. This outcome occurred in 13% of patients treated with atorvastatin and in 29% of those who received placebo, a significant difference.
- The atorvastatin and placebo arms showed no significant differences in adverse events during the study, with roughly similar incidence rates for muscle pain, elevated liver enzymes, and renal failure. None of the enrolled patients developed myositis.
- Atorvastatin treatment also produced an expected average 37% decline from baseline in levels of LDL cholesterol.
- "This was a well-designed and important trial," said Dr. Witteles. "Anthracyclines remain a mainstay of cancer therapies for a number of malignancies, such as lymphoma and sarcoma, and the cardiac side effects of development of cardiac dysfunction are unequivocally real."

- The importance of a clinically meaningful effect
- The results especially contrast with the findings from the PREVENT study, published in 2022, which compared a daily, 40-mg atorvastatin treatment with placebo in 279 randomized patients with breast cancer and treated for 24 months. However, patients in PREVENT had a cumulative, median anthracycline dose of 240 mg/m^2, and the study's primary outcome was the average change from baseline in LVEF after 24 months of treatment, which was a reduction of 0.08 percentage points in the placebo arm, a nonsignificant difference.
- In STOP-CA, the average change in LVEF from baseline was a 1–percentage point reduction in the placebo arm, compared with the atorvastatin-treated patients, a difference that was statistically significant, but "not clinically significant," said Dr. Neilan, director of the cardio-oncology program at Massachusetts General Hospital, Boston. He cited the good fortune of the STOP-CA investigators when they received a recommendation from reviewers early on to design their study to track a clinically meaningful change in LVEF rather than just looking at the average overall change.
- Dr. Deswal also noted that it is unlikely that future studies will examine the efficacy of a statin for preventing LVEF in patients across the range of cancers that are eligible for anthracycline treatment. As a result, she predicted that "we may have to extrapolate" the results from STOP-CA to patients with other cancer types.
- STOP-CA received no commercial funding. Dr. Neilan has been a consultant for and received fees from Abbvie, Amgen, Bristol-Myers Squibb, CRC Oncology, Genentech, Roche, and Sanofi, and has received grant funding from AstraZeneca and Bristol Myers Squib. Dr. Deswal and Dr. Witteles had no relevant disclosures.
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Bempedoic Acid Cuts CV Events in Statin-Intolerant Patients: CLEAR Outcomes

- A new approach to lowering cholesterol with the use of bempedoic acid (*Nexletol*, Esperion) brought about a significant reduction in cardiovascular events in patients intolerant to statins in the large phase 3 placebo-controlled CLEAR Outcomes trial.
- The drug lowered LDL cholesterol by 21% in the study and reduced the composite primary endpoint, including cardiovascular death, myocardial infarction (MI), stroke, or coronary revascularization, by 13%; MI was reduced by 23% and coronary revascularization, by 19%.
- The drug was also well-tolerated in the mixed population of primary and secondary prevention patients unable or unwilling to take statins.
- "These findings establish bempedoic acid as an effective approach to reduce major cardiovascular events in statin-intolerant patients," study chair, Steve Nissen, MD, Cleveland Clinic, Ohio, concluded.
- Nissen presented the CLEAR Outcomes trial on March 4 at the American College of Cardiology (ACC) Scientific Session/World Congress of Cardiology (WCC) 2023.

- The study was simultaneously published online in the *New England Journal of Medicine (NEJM)*. Topline results were previously reported in December 2022.
- Nissen pointed out that while in the current study bempedoic acid was studied as monotherapy, he believes the drug will mainly be used in clinical practice in combination with ezetimibe, a combination shown to reduce LDL by 38%. "I think this is how it will be used in clinical practice. So, we can get an almost 40% LDL reduction — that's about the same as 40 mg simvastatin or 20 mg atorvastatin — without giving a statin. And I think that's where I see the potential of this therapy," he commented.
- Nissen described statin intolerance as "a vexing problem" that prevents many patients from achieving LDL cholesterol levels associated with cardiovascular benefits.
- He explained that bempedoic acid, an adenosine triphosphate citrate lyase inhibitor, inhibits hepatic cholesterol synthesis upstream of hydroxymethylglutaryl coenzyme A reductase, the enzyme inhibited by statins. Bempedoic acid is a pro-drug activated in the liver, but not in peripheral tissues, resulting in a low incidence of muscle-related adverse events. Although bempedoic acid is approved for lowering LDL cholesterol, this is the first trial to assess its effects on cardiovascular outcomes.
- The CLEAR Outcomes trial included 13,970 patients (48% women) from 32 countries who were unable or unwilling to take statins owing to unacceptable adverse effects and who had, or were at high risk for, cardiovascular disease. They were randomly assigned to oral bempedoic acid, 180 mg daily, or placebo.
- The mean LDL cholesterol level at baseline was 139 mg/dL in both groups, and after 6 months, the reduction in the level was greater with bempedoic acid than with placebo by 29.2 mg/dL (a 21.1% reduction).
- The drug was also associated with a 22% reduction in high-sensitivity C-reactive protein.

- After a median duration of follow-up of 40.6 months, the incidence of a primary end point (cardiovascular death, MI, stroke, or coronary revascularization) was significantly lower (by 13%) with bempedoic acid than with placebo (11.7% vs 13.3%; hazard ratio, 0.87; *P* = .004).
- The absolute risk reduction was 1.6 percentage points, and the number needed to treat for 40 months to prevent one event was 63.
- The secondary composite endpoint of cardiovascular death/stroke/MI was reduced by 15% (8.2% vs 9.5%; hazard ratio, 0.85; *P* = .006).
- Fatal or nonfatal MI was reduced by 23% (3.7% vs 4.8%; hazard ratio, 0.77; *P* = .002), and coronary revascularization was reduced by 19% (6.2% vs 7.6%; hazard ratio, 0.81; *P* = .001).
- Bempedoic acid had no significant effects on fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause.
- Subgroup analysis showed similar results across all groups and no difference in treatment effect between men and women.
- Adverse events were reported by 25% of patients in both groups, with adverse events leading to discontinuation reported by 10.8% of the bempedoic acid group and 10.4% of the placebo group.
- Muscle disorders were reported in 15.0% of the bempedoic acid group vs 15.4% of the placebo group. And there was also no difference in new cases of diabetes (16.1% vs 17.1%).

- Bempedoic acid was associated with small increases in the incidence of gout (3.1% vs 2.1%) and cholelithiasis (2.2% vs 1.2%), and also small increases in serum creatinine, uric acid, and hepatic enzyme levels.
- In the *NEJM* article, the authors point out that the concept of statin intolerance remains controversial. Some recent studies suggested that reported adverse effects represent an anticipation of harm, often described as the "nocebo" effect.
- "Whether real or perceived, statin intolerance remains a vexing clinical problem that can prevent patients who are guideline-eligible for statin treatment from reaching LDL cholesterol levels associated with clinical benefits. Accordingly, alternative non-statin therapies are needed to manage the LDL cholesterol level in these patients," they write.
- "Management of patients unable or unwilling to take statins represents a challenging and frustrating clinical issue. Regardless whether this problem represents the 'nocebo' effect or actual intolerance, these high-risk patients need effective alternative therapies," Nissen concluded. "The CLEAR Outcomes trial provides a sound rationale for use of bempedoic acid to reduce major adverse cardiovascular outcomes in patients intolerant to statins."

- "Compelling Findings"
- Discussing the trial at the ACC late-breaking clinical trial session, Michelle O'Donoghue, MD, Brigham and Women's Hospital, Boston, Massachusetts, noted that this is the largest trial to date in statin-intolerant patients.
- She pointed out that although the issue of statin intolerance remains controversial, adherence to statins is often not good, so this is an important patient population to study.
- She said it was "quite remarkable" that 48% of the study were women, adding, "There is still much that we need to understand about why women appear to be less willing or able to tolerate statin therapy."
- O'Donoghue concluded that the study showed "compelling findings," and the event reduction was in line with what would be expected from the LDL cholesterol reduction, further supporting the LDL hypothesis.
- She added that: "Bempedoic acid is an important addition to our arsenal of nonstatin LDL-lowering therapies. And while it was overall well tolerated, it did not get a complete free pass, as there were some modest safety concerns."
- In an editorial accompanying the *NEJM* publication, John Alexander, MD, Duke Clinical Research Institute, Durham, North Carolina, writes, "The compelling results of the CLEAR Outcomes trial will and should increase the use of bempedoic acid in patients with established atherosclerotic vascular disease and in those at high risk for vascular disease who are unable or unwilling to take statins."

- He warns, however, that it is premature to consider bempedoic acid as an alternative to statins. "Given the overwhelming evidence of the vascular benefits of statins, clinicians should continue their efforts to prescribe them at the maximum tolerated doses for appropriate patients, including those who may have discontinued statins because of presumed side effects," he writes.
- Alexander also points out that although bempedoic acid also reduces the LDL cholesterol level in patients taking statins, the clinical benefits of bempedoic acid added to standard statin therapy are unknown.
- On the observation that bempedoic acid had no observed effect on mortality, he notes that "Many individual trials of statins have also not shown an effect of the agent on mortality; it was only through the meta-analysis of multiple clinical trials that the effects of statins on mortality became clear."
- "Bempedoic acid has now entered the list of evidence-based alternatives to statins for primary and secondary prevention in patients at high cardiovascular risk," Alexander concludes. "The benefits of bempedoic acid are now clearer, and it is now our responsibility to translate this information into better primary and secondary prevention for more at-risk patients, who will, as a result, benefit from fewer cardiovascular events."
- In a second editorial, John F. Keaney Jr, MD, Brigham and Women's Hospital, says the lack of a clear association between bempedoic acid and muscle disorders, new-onset diabetes, or worsening hyperglycemia is "welcome news" for statin-intolerant patients.

- But he cautions that "These data must be interpreted cautiously, because bempedoic acid, when combined with a statin, appears to enhance the occurrence of muscle symptoms. Moreover, bempedoic acid has its own reported side effects, including tendon rupture, increased uric acid levels, gout, and reduced glomerular filtration rate, which are not seen with statin use."
- In terms of drug interactions, Keaney notes that bempedoic acid can increase the circulating levels of simvastatin and pravastatin, so it should not be used in patients who are receiving these agents at doses above 20 mg and 40 mg, respectively. Similarly, bempedoic acid should not be used with fibrates other than fenofibrate because of concerns regarding cholelithiasis.
- "Available data clearly indicate that bempedoic acid can be used as an adjunct to statin and nonstatin therapies (except as noted above) to produce an additional 16 to 26% reduction in the LDL cholesterol level," he adds. "However, it is not yet clear to what extent adjunctive bempedoic acid will further reduce the risk of cardiovascular events."

'Breakthrough' Study: Diabetes Drug Helps Prevent Long COVID

Carolyn Crist

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WebMD

- Metformin appears to play a role in preventing long COVID when taken early during a COVID-19 infection, according to a new preprint study from *The Lancet*. The preprint hasn't yet been peer-reviewed or published in a journal.
- In particular, metformin led to a 42% drop in long COVID among people who had a mild to moderate COVID-19 infection.
- "Long COVID affects millions of people, and preventing long COVID through a treatment like metformin could prevent significant disruptions in people's lives," says lead author Carolyn Bramante, MD, an assistant professor of internal medicine and pediatrics at the University of Minnesota.
- Between January 2021 and February 2022, Bramante and colleagues tested three oral medications – metformin (typically used to treat type 2 diabetes), ivermectin (an antiparasitic), and fluvoxamine (an antidepressant) – in a clinical trial across the U.S. called COVID-OUT. The people being studied, investigators, care providers, and others involved in the study were blinded to the randomized treatments. The trial was decentralized, with no in-person contact with participants.

- The researchers included patients who were ages 30-85 with overweight or obesity, had documentation of a confirmed COVID-19 infection, had fewer than 7 days of symptoms, had no known prior infection, and joined the study within 3 days of their positive test. The study included monthly follow-up for 300 days, and participants indicated whether they received a long COVID diagnosis from a medical doctor, which the researchers confirmed in medical records after participants gave consent.
- The medications were pre-packaged into pill boxes for fast delivery to participants and to ensure they took the correct number of each type of pill. The packages were sent via same-day courier or overnight shipping.

- The metformin doses were doled out over 14 days: with 500 milligrams on the first day, 500 milligrams twice a day for the next 4 days, and then 500 milligrams in the morning and 1,000 milligrams in the evening for the remaining 9 days.
- Among the 1,323 people studied, 1,125 agreed to do long-term follow-up for long COVID, including 564 in the metformin group and 561 in the blinded placebo group. The average age was 45, and 56% were women, including 7% who were pregnant.
- The average time from the start of symptoms to starting medication was 5 days, and 47% began taking the drug within 4 days or less. About 55% had received the primary COVID-19 vaccination series, including 5.1% who received an initial booster, before enrolling in the study.
- Overall, 8.4% of participants reported that a medical provider diagnosed them with long COVID. Of those who took metformin, 6.3% developed long COVID, compared to 10.6% among those who took the identical-matched placebo.

- The risk reduction for metformin was 42% versus the placebo, which was consistent across subgroups, including vaccination status and different COVID-19 variants.
- When metformin was started less than 4 days after COVID-19 symptoms started, the effect was potentially even greater, with a 64% reduction, as compared with a 36% reduction among those who started metformin after 4 or more days after symptoms.
- Neither ivermectin nor fluvoxamine showed any benefits for preventing long COVID.
- At the same time, the study authors caution that more research is needed.
- "The COVID-OUT trial does not indicate whether or not metformin would be effective at preventing long COVID if started at the time of emergency department visit or hospitalization for COVID-19, nor whether metformin would be effective as treatment in persons who already have long COVID," they wrote. "With the burden of long COVID on society, confirmation is urgently needed in a trial that addresses our study's limitations in order to translate these results into practice and policy.“
- Several risk factors for long COVID emerged in the analysis. About 11.1% of the women had a long COVID diagnosis, as compared with 4.9% of the men. Also, those who had received at least the primary vaccine series had a lower risk of developing long COVID, at 6.6%, as compared with 10.5% among the unvaccinated. Only one of the 57 people who received a booster shot developed long COVID.
- Notably, pregnant and lactating people were included in this study, which is important given that pregnant people face higher risks for poor COVID-19 outcomes and are excluded from most non-obstetric clinical trials, the study authors wrote. In this study, they were randomized to metformin or placebo but not ivermectin or fluvoxamine due to limited research about the safety of those drugs during pregnancy and lactation.

- The results are now under journal review but show consistent findings from other recent studies. Also, in August 2022, the authors published results from COVID-OUT that showed metformin led to a 42% reduction in hospital visits, emergency department visits, and deaths related to severe COVID-19.
- "Given the lack of side effects and cost for a 2-week course, I think these data support use of metformin now," says Eric Topol, MD, founder and director of the Scripps Research Translational Institute and editor-in-chief of Medscape, WebMD's sister site for health care professionals.
- Topol, who wasn't involved with this study, has been a leading voice on COVID-19 research throughout the pandemic. He noted the need for more studies, including a factorial design trial to test metformin and Paxlovid, which has shown promise in preventing long COVID. Topol also wrote about the preprint in *Ground Truths*, his online newsletter.
- "As I've written in the past, I don't use the term 'breakthrough' lightly," he wrote. "But to see such a pronounced benefit in the current randomized trial of metformin, in the context of it being so safe and low cost, I'd give it a breakthrough categorization."
- Another way to put it, Topol wrote, is that based on this study, he himself would take metformin if he became infected with COVID-19.
- Jeremy Faust, MD, an emergency medicine doctor at Brigham and Women's Hospital in Boston, also wrote about the study in his newsletter, *Inside Medicine*. He noted that the 42% reduction in long COVID means that 23 COVID-19 patients need to be treated with metformin to prevent one long COVID diagnosis, which is an "important reduction."
- "Bottom line: If a person who meets criteria for obesity or overweight status were to ask me if they should take metformin (for 2 weeks) starting as soon as they learn they have COVID-19, I would say *yes* in many if not most cases, based on this new data," he wrote. "This is starting to look like a real win."

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Thanks for attention