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Gut 2018 Aug 14

Glutamine for Treatment of Postinfectious Irritable Bowel Syndrome

A dietary supplement may improve persistent gastrointestinal symptoms after enteric infection.

Patients with infectious enteritis are at increased risk for developing irritable bowel syndrome (IBS) after resolution of the acute infection. Glutamine is an essential amino acid and one of its key functions is maintenance of the barrier function of the intestine. Patients with postinfectious IBS diarrhea-predominant (IBS-D) have high prevalence of intestinal hyperpermeability.

In the current double-blinded, randomized, controlled trial (RCT), investigators tested the hypothesis that glutamine supplementation could restore normal intestinal permeability and ameliorate persistent gastrointestinal symptoms in patients with postinfectious IBS-D. One hundred and fifteen patients were randomized to receive 5 g of oral glutamine powder or placebo powder (whey protein with similar characteristics) three times daily for 8 weeks.

Increased intestinal permeability was defined as elevated urinary lactulose/mannitol ratio (≥0.07). The primary endpoint was a reduction of ≥50 points on the IBS Symptom Severity Scale. Secondary endpoints

included changes in daily bowel movement frequency, stool form as measured by the Bristol Stool Scale, and intestinal permeability.

Nearly 80% of the glutamine group achieved the primary endpoint, compared with 6% of patients who received placebo. Glutamine also significantly reduced daily bowel movement frequency (3 vs. 5) and Bristol Stool Scale scores (4 vs. 6.5) and normalized intestinal permeability. Adverse events were infrequent (abdominal pain and bloating were the most common, at rates of 2% in each group), and no serious adverse events occurred.

COMMENT: The results of this double-blinded RCT are impressive, although the sample size was small and apparently empirical. Nevertheless, the objective improvement in intestinal permeability suggests that glutamine may be a viable option for some patients with postinfectious IBS-D and warrants larger and adequately powered RCTs in patients with other types of IBS-D.

CITATION(S): Zhou Q et al. Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. Gut 2018 Aug 14; [e-pub]. (https://gut.bmj.com/content/early/2018/08/14/gutjnl-2017-315136)

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.Pediatrics 2018 Sep; 142:e20181076

Marijuana Use While Breast-Feeding — What's in Mother's Milk?

Analysis revealed substantial levels of cannabis metabolites.

Marijuana is the most commonly used recreational drug in pregnant and breast-feeding women; however, the neurobehavioral risks to infants exposed to cannabis in breast milk remain unknown. In a study involving 50 breast-feeding mothers who reported marijuana use, researchers in California measured cannabinoid concentrations in 54 samples of breast milk to determine the relation between the mother's most recent use of marijuana and the potential dosage to her infant. Thirty-two participants (64%) used inhalation as the only means of administration; 44 reported at least daily use.

Cannabis metabolites were found in all samples, with higher concentrations in those from women who exclusively used inhalation. The psychoactive ingredient in marijuana, Δ-9-tetrahydrocannabinol (Δ-9-THC), was detected in 34 samples (63%). There was a strong correlation between Δ-9-THC concentrations in breast milk and hours since last marijuana use. The half-life of Δ-9-THC was estimated to be 27 hours, implying that clearing the drug from human milk could take about 6 days (5 half-lives).

COMMENT: Cannabis metabolites are highly lipophilic, so it makes sense that they would be found in the fat of human milk — and probably also in the fat-rich infantile brain. Accordingly, the potential effects of these metabolites on the developing infant brain are of the utmost concern. The next step will be to measure concentrations of cannabinoid metabolites in infant plasma and correlate these levels with developmental outcomes. It's still most prudent to urge pregnant and breast-feeding women to abstain from inhaling or ingesting any marijuana or cannabis products.

CITATION(S): Bertrand KA et al. Marijuana use by breastfeeding mothers and cannabinoid concentrations in breast milk. Pediatrics 2018 Sep; 142:e20181076. (https://doi.org/10.1542/peds.2018-1076)

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STI Rates Climb for Fourth Straight Year

Worrisome data underscore the apparent backward direction of the U.S. in controlling sexually transmitted infections.

U.S. rates of gonorrhea, chlamydia, and syphilis have all steeply increased for the fourth consecutive year, according to preliminary data from the CDC. Nearly 2.3 million cases of those sexually transmitted infections (STIs) were diagnosed in 2017, an increase of 200,000 over the prior year. Among the other findings:

- Incident gonorrhea has increased 67% — from 333,000 to 556,000 — from 2013 to 2017. Among men, the number nearly doubled. Of note, in lab testing, emerging resistance to azithromycin rose from 1% to 4% from 2013 to 2017. Azithromycin is often coadministered with ceftriaxone to delay resistance to ceftriaxone.
- Cases of primary and secondary syphilis increased 76% — from 17,000 to 30,000 — during these 4 years.
- Cases of chlamydia have hit 1.7 million, nearly half were among young females aged 15 to 24.

COMMENT: *Anna Wald, MD, MPH*

These data underscore the apparent backward direction of the U.S. in controlling STIs. While most cases of syphilis have been among men who have sex with men, the epidemic is also starting to affect women, with an attendant increase in congenital syphilis contributing to the recent decline in U.S. maternal child health. It's difficult to parse the contributions of changes in sexual behavior versus poor access to care; undoubtedly, however, slashes to funding for public health clinics (including Planned Parenthood) have been deleterious.

CITATION(S): Centers for Disease Control and Prevention — National Center for HIV/AIDS Viral Hepatitis, STD, and TB Prevention [news release]. New CDC analysis shows steep and sustained increases in STDs in recent years. Aug 18 2018. (https://www.cdc.gov/nchhstp/newsroom/2018/press-release-2018-std-prevention-conference.html)

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Transl Psychiatry 2018 Aug 1; 8:136

Children of Mothers with PCOS Have Increased Risk for Autism

Also, in unadjusted analyses, women with PCOS had an increased risk for autism, and people with autism had a higher risk for PCOS.

Both male and female patients with autism spectrum disorder (ASD) have elevated androgen levels, and ASD rates are higher in males than females (Psychoneuroendocrinology 2011; 36:1154).These findings have led to research into fetal androgenic effects and ASD risk. The hyperandrogenism in polycystic ovary syndrome (PCOS) has similarly led to questions about ASD risks in offspring of women with PCOS, PCOS risk in women with ASD, and ASD risk in women with PCOS. To study these issues, researchers used U.K. general practitioner records, which essentially capture the U.K. population, to perform a series of investigations.

In one study, the risk for ASD in adjusted analyses was significantly raised in first-born offspring of 8588 mothers with PCOS, compared with offspring of 41,127 matched control mothers (odds ratio 1.35). In another study, ASD risk was almost doubled in 26,263 women with PCOS, compared with 130,717 women without PCOS (OR, 1.9). Finally, PCOS risk was elevated in 971 women with ASD, compared with 4855 women without ASD (OR, 2.0). However, in the last two studies, results were not significant after adjusting for psychiatric comorbidities and strict PCOS diagnoses.

COMMENT: Informing women with PCOS about their offspring's elevated ASD risk may motivate women to treat their own often-associated obesity, which is especially important because ASD risk is almost twice as high in children of obese women with PCOS (NEJM JW Psychiatry Feb 2016 and Mol Psychiatry 2016; 21:1441). Also, women with PCOS need evaluation for ASD, and women with ASD need evaluation for PCOS.

These findings strengthen the argument against valproate use in women of childbearing age. Not only does valproate have teratogenic effects, but also PCOS risk likely increases during valproate treatment (Curr Psychiatry Rep 2017; 19:58).

CITATION(S): Cherskov A et al. Polycystic ovary syndrome and autism: A test of the prenatal sex steroid theory. Transl Psychiatry 2018 Aug 1; 8:136. (https://doi.org/10.1038/s41398-018-0186-7)

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Pediatrics 2018 Sep 10

Conversations Between Parents and Toddlers Help Build Intelligence and Vocabulary

Turn-taking language interactions at children's ages 18 to 24 months were strongly linked with higher IQ and language scores through middle-school age.

Several studies show that the quality and quantity of parent-child language interaction in the early years predict later school achievement and language abilities up to third grade entry. Now, researchers have examined whether the amount of such interaction at children's ages 2 to 36 months has a longer-term effect on their development and language skills — at elementary-school to middle-school ages.

In this longitudinal study, at baseline, day-long audio recordings were made of parents and children at home once monthly for 6 months. These were analyzed for the number of adult words and adult-child

conversational turns. At 10-year follow-up, 146 children (age range, 9 to 13 years) underwent intelligence and language testing.

Even after adjusting for socioeconomic status and children's baseline language skills, investigators found that adult word count and conversational turn count predicted children's language test scores through middle-school age. The strongest effects on IQ, verbal comprehension, and vocabulary were seen for conversational turn counts during the 18- to 24-month age window — a time of "language explosion" in children.

COMMENT: The editorialists note that primary care offers a "low-cost platform for universal, population-level prevention through relationship- and strengths-based strategies" such as Reach Out and Read. As a trusted source of information for parents, pediatric clinicians can promote language-rich environments by encouraging: (1) talking, singing, reading, and asking questions *before* the crucial 18- to 24-month window; (2) turning off background TV and media devices that distract from language exchanges; and (3) signing up for information from programs such as TalkingIsTeaching.org that can e-mail or text parents tips for positive everyday interactions.

CITATION(S): Gilkerson J et al. Language experience in the second year of life and language outcomes in late childhood. Pediatrics 2018 Sep 10; [e-pub]. (https://doi.org/10.1542/peds.2017-4276)

Mendelsohn AL and Klass P. Early language exposure and middle school language and IQ: Implications for primary prevention. Pediatrics 2018 Sep 10; [e-pub]. (https://doi.org/10.1542/peds.2018-2234)

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Lancet 2018 Aug 11; 392:477

Type 1 Diabetes: The Earlier the Onset, the Worse the Prognosis

Data from a Swedish registry study emphasize the need to focus on early-onset patients' elevated cardiovascular risks and mortality.

Many questions persist about the excess mortality and cardiovascular risk in young adults with type 1 diabetes, particularly with regard to age at diabetes onset. Investigators addressed this issue with an analysis of 27,195 patients with type 1diabetes identified in the Swedish National Diabetes Register and 135,178 nondiabetes controls matched by age, sex, and county from the general Swedish population.

The glycated hemoglobin (HbA1c) values were higher in patients with younger age at onset (diagnosis at 0–10 years) than those with later onset (diagnosis at ages 26–30). At a median follow-up of 10 years, there were 959 deaths in the diabetes group and 1501 in the control group. Compared with controls, people with early onset of diabetes had markedly increased risks for all-cause mortality (hazard ratio [HR], 4.11); cardiovascular disease (HR, 11.44); acute myocardial infarction (HR, 30.95); and heart failure (HR, 12.90) among other outcomes. Patients with later onset had rates higher than controls but lower than patients with early onset. Risk was up to five times greater in those with early versus later onset. Early-onset diabetes was associated with a loss of 18 life-years in women and 14 life-years in men.

COMMENT: These results bring home several key points. The association of type 1 diabetes with adverse prognoses depends strongly on the age of onset. This distinction ought to be incorporated into risk scores and decision making. Also, we ought to be focusing particularly on patients with early onset to determine how we can best mitigate their risk, with implications for lifestyle, treatment, screening, and monitoring.

CITATION(S): Rawshani A et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: A nationwide, register-based cohort study. Lancet 2018 Aug 11; 392:477. (https://doi.org/10.1016/S0140-6736(18)31506-X)

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Hospitals Fed Up with Drug Companies are Starting Their Own

A group of major American hospitals, battered by price spikes on old drugs and long-lasting shortages of critical medicines, has launched a mission-driven, not-for-profit generic drug company, Civica Rx, to take some control over the drug supply.

This effort is backed by seven large health systems and three philanthropic groups and will be led by an industry insider. The company will focus initially on establishing price transparency and stable supplies for 14 generic drugs used in hospitals, without pressure from shareholders to issue dividends or push a stock price higher.

https://www.washingtonpost.com/national/health-science/hospitals-are-fed-up-with-drug-companies-so-theyre-starting-their-own/2018/09/05/61c27ec4-b111-11e8-9a6a-565d92a3585d_story.html?noredirect=on&utm_term=.41ce7351abfa

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FDA Commissioner on Product Quality at Foreign Drug Manufacturing Sites

The shift to overseas production of U.S. goods, including some drugs and their components, predominantly occurred in the early 2000s and has added new complexities to the U.S. drug-supply chain. Consequently, the FDA has taken different steps to address the issue.

To add greater transparency, the FDA is publishing their internal policy for how manufacturing facilities are prioritized and scheduled for surveillance inspections. The policy explains how a facility's compliance history, recall trends, time since last inspection, inherent risk of the drug being manufactured, processing complexity, and other factors are all weighed and considered.

The FDA prioritizes inspections of sites regardless of their location. For manufacturing facilities in other countries, inspections may be conducted by staff in foreign offices, those on temporary duty assignments, or staff who travels internationally to conduct the inspection. In addition, to maximize resources and efficiency, the FDA has also pursued opportunities to collaborate with other countries. With the announcement last year concerning the Mutual Recognition Agreement with the EU, they have ensured that the FDA can recognize the drug inspections conducted by foreign

regulatory authorities that meet U.S. requirements. In doing so, the FDA is able to dedicate more of their investigators' time to those sites that pose the greatest risk.

https://www.pharmoutsourcing.com/1315-News/353295-Statement-from-FDA-Commissioner-on-Product-Quality-at-Foreign-Drug-Manufacturing-Facilities/

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N Engl J Med 2018 Aug 9; 379:513

Elective Induction of Labor at Term: Has Its Time Arrived?

In low-risk nulliparous women, compared with expectant management, labor induction at 39 weeks was associated with lower likelihood of cesarean delivery.

Obstetric practice has long held that elective induction of labor is inadvisable because it raises risk for cesarean delivery. This dictum was based on observational data assessing outcomes of induced versus spontaneous labor, a comparison that is not clinically pertinent: In real-world practice, the decision is between labor induction and expectant management. In a multicenter U.S.-based randomized trial, investigators have examined these strategies head to head, with a focus on risk for cesarean delivery and a composite outcome of perinatal harm. Some 22,000 nulliparous women at low risk for adverse obstetric outcomes were invited to participate; of these, 71% declined, leaving a cohort of 6100 women randomly assigned to labor induction (at 39 weeks 0 days to 39 weeks 4 days) or expectant management (until 40 weeks 5 days to 42 weeks 2 days).

Risk for perinatal harm was 20% lower in the induction of labor group (4.3% vs. 5.4%, driven largely by a lower risk for respiratory support), although this result did not meet the prespecified threshold for a clinically meaningful difference. Rates of cesarean delivery were 19% (induction) versus 22% (expectant management; $P<0.001$). Incidence of hypertensive disorders of pregnancy was also lower in the induction group.

COMMENT: These long-awaited data convincingly demonstrate that labor induction at 39 weeks' gestation (in the absence of medical indications for delivery) does not result in harm, including excess risk for cesarean delivery — at least among women similar to the trial participants. Criticism stems from the many women who declined trial participation and the resultant skewed demographics of the study population (younger and less likely to be white) compared with the general U.S. population of pregnant women. Concerns about generalizability aside, I plan to tell patients who inquire about elective labor induction that clinicians can no longer argue against the practice out of concern that it might be harmful.

CITATION(S): Grobman WA et al. Labor induction versus expectant management in low-risk nulliparous women. N Engl J Med 2018 Aug 9; 379:513. (https://doi.org/10.1056/NEJMoa1800566)

Greene MF. Choices in managing full-term pregnancy. N Engl J Med 2018 Aug 9; 379:580. (https://doi.org/10.1056/NEJMe1807747)

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Arch Womens Ment Health 2018 Jul 14

Epidemiology of Postpartum Depression: An Unexpected Finding

In Sweden, depressive episodes within the first year of delivery did not cluster around the postpartum period.

Whether postpartum depression (PPD) is a separate entity or occurs within the natural course of depression remains uncertain. Prior investigatory attempts had limitations, with most studies not including comparisons to depression incidence at other times and lacking clinical diagnoses or medical record verification of recurrent depression, a known risk factor for PPD. To overcome these limitations, investigators used Swedish birth and medical registries of 707,701 mothers with first live singleton births to examine whether women with and without PPD histories have similar rates of depression within 12 months of delivery.

Using a random date derived from the mean delivery dates of similarly aged women (either >12 months before or >3 months after the birth), researchers found that the 12-month incidence of depression was similar in 4397 women with PPD histories and in 4687 women without PPD but with histories of depression at other times (relative risks compared with nondepressed women, 21 and 26, respectively). Of note, 34% of women with PPD had recurrent depression histories — similar to rates in other studies.

COMMENT: These results support the concept that PPD is an episode of depression occurring coincidentally after birth and bolster the authors' hypothesis that PPD prevalence seems high because pregnant women are a medically captured group.

Biological investigations, however, argue against this interpretation. After birth, levels of pregnanolone (a GABA modulator) drop precipitously. This knowledge was the premise for intravenous treatment of PPD with an experimental version of pregnanolone, which produced significant improvement (Lancet 2017; 390:480). Also, precipitous drops in estrogen after birth are associated with marked monoamine oxidase A increases, which are evident on positron-emission tomography scanning of brain regions associated with depression (JAMA Psychiatry 2010; 67:468). Future research is needed to unravel the disparate epidemiological and biological findings.

CITATION(S): Silverman ME et al. Is depression more likely following childbirth? A population-based study. Arch Womens Ment Health 2018 Jul 14; [e-pub]. (https://doi.org/10.1007/s00737-018-0891-5)

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BMJ 2018 Jul 11; 362:k2644

IVF and Cancer Risk: A Nuanced Association

IVF treatment was not associated with excess risk for invasive breast or uterine corpus cancer, but it was associated with risk for ovarian cancer in women with endometriosis who remained nulliparous after IVF.

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The relation between in vitro fertilization (IVF) and women's cancer remains unclear. Investigators explored risk for cancer of the breast, uterine corpus, and ovary in 226,000 British women who underwent IVF from 1991 to 2010 (mean age at IVF, 35; median follow-up, 9 years) compared with the female population of England and Wales.

IVF was not associated with excess risk for invasive breast cancer or uterine corpus cancer, but it was associated with modestly increased risk for in situ breast cancer (standardized incidence ratio [SIR], 1.15; absolute excess risk, 1.7 cases per 100,000 person-years). IVF was not associated with excess risk for ovarian cancer (borderline or invasive) in women without endometriosis who achieved live birth (SIR, 1.03); however, risk was increased among women with endometriosis who remained nulliparous following IVF (SIR, 2.24).

COMMENT: As the authors note, their study is limited by the fact that the comparator group consisted of the female population of England and Wales rather than infertile women who did not have IVF treatment. Women undergoing IVF differ from the general population regarding parity and endometriosis, both known risk factors for ovarian cancer (NEJM JW Womens Health May 24 2018; [e-pub] and *Obstet Gynecol* 2018 Jun; 131:1095). This study provides reassurance that IVF treatment is not associated with significantly increased risk for invasive breast cancer or uterine corpus cancer. However, the results point to an association with ovarian cancer among women with endometriosis and those who do not achieve live birth after IVF treatment.

CITATION(S): Williams CL et al. Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991–2010: Data linkage study including 2.2 million person years of observation. BMJ 2018 Jul 11; 362:k2644. (https://doi.org/10.1136/bmj.k2644)