EDITORIAL

Consumption of Nonnutritive Sweeteners during Pregnancy

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Introduction

Studies have indicated that practically all pregnant ladies in the world have certain degree of synthetic compounds in their body, for example, phthalates, bisphenol A, flame retardant, tobacco, pesticides, lead, polychlorinated-biphenyl, and mercury.[1,2] These synthetic compounds have been related to preterm birth, innate peculiarities, and neuroformative issues. During early fetal advancement, even gentle introduction to such poisonous synthetic concoctions can have enduring negative impacts prompting development of infection from youth to adulthood.[1,3]

Among developing food additive substances that are raising concerns, nonnutritive sugars (NNS) have been tested in kids, grown-ups, and pregnant women.[4,5]

Nonnutritive Sweeteners and Nonnutritive Sugars Regulation and Labeling

Nonnutritive sugars (NNS) are zero or low-calorie options in contrast to nutritive sugars. They are generally utilized in nourishments and drinks.[6] Right now, there are no rules for NNS utilization in pregnancy, despite collecting proof of unfriendly impacts, after their utilization, in creature models. The American Heart Association suggest restricting included sugar by supplanting it with without sugar choices containing NNS. NNS endorsed for utilization in the United States are Sucralose, Acesulfame-K, Aspartame, Saccharin, and Stevioside.[4] Accordingly, NNS use has been accounted for to have expanded from 8.7% to 25.1% in kids and from 26.9% to 41.4% of grown-ups from 1999 to 2000 to 2009 to 2012, with higher utilization in females than males.[7] The FDA has approved six NNS and has given ADI (Acceptable Daily Intake) values for each.[8]

The two difficulties that purchasers are looking after the endorsement by FDA are that initially, NNS amount is not uncovered per serving on huge numbers of the foods and refreshments, and furthermore, NNS is additionally being found in clueless items, for example, 'no-sugar included' or 'decreased sugar' items, making it hard for buyers to maintain a strategic distance from NNS.

Sugar items with NNS answers to bring down rewards in the sensory system contrasted with sweet nourishments or drinks.[9] NNS binds to sweet taste receptors that are found on the tongue as well as in the lungs, digestion tracts, fat tissues, bones, and testicles.[10,11]

Consequences of Nonnutritive Sugars Consumption in Animals and Humans

Nonnutritive sugars once bound to sweet receptor can trigger insulin increase in people.[12–14] It modifies the release of incretin; in this way, when NNS is co-ingested alongside glucose, it builds the measure of glucose retained.[15–18] NNS likewise upregulates adipogenesis promoting pathways.[19,20] They decline the degree of useful microbes in the body. Saccharin, Aspartame, and Sucralose have bacteriostatic impact on oral microorganisms.[21] Saccharin and Acesulfame-K invigorate adipogenesis through AKT (protein kinase B) flagging.[19]

In human investigations, NNS has appeared to bring down BMI in overweight kids and incomprehensibly expands BMI in normal weight kids and builds the danger of metabolic disorder in grown-ups.[22–24]

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Consequences of Nonnutritive Sugars Consumption in Animals and Humans

Nonnutritive Sugars Absorption, Distribution, and Excretion during Pregnancy and Lactation

Nonnutritive sugars is adsorbed from the small digestive tract into the circulatory system and is moved to the baby through the placenta and into a newborn child through breastmilk. Some NNS are completely metabolized through others are discharged unmetabolized in the urine, feces, and blood. Sucralose is consumed into the circulatory system and is found in the urine for around 5 days after the day of ingestion. Acesulfame-K is not processed or put away and however discharged out of the system as urine.[25] Saccharin is not processed in the system.[26] While its greater part is retained, rest of it is disposed of urine, feces, and so forth. Aspartame goes through full assimilation in the GIT giving secondary metabolites, which are invested in the circulatory system.[27] Individuals with phenylketonuria, an uncommon inherited disorder, experience issues in utilizing aspartame breakdown item phenylalanine and ought to hence avoid aspartame.[28] Steviosides are processed by gut microscopic organisms.[29,30]

In utero Exposure and Breastmilk

Studies have shown that sucralose can be found in the urine of the newborns proposing *in utero* transmission through cord blood.[31] Acesulfame-K was found in amniotic liquids and urine of fetus in

any event when high focuses were found in the placenta proposing NNS filtering.[31,32] Saccharin was found in amniotic fluid and fetal bladder just as maternal blood in same amounts.[33] Aspartame was not found to go through placenta, since it is completely processed in the GIT.[28] Sucralose, Acesulfame-K, and Saccharin can be transferred through breastmilk.[34,35] Aspartame is anyway not found in the breastmilk.[34]

Safety of Perinatal Nonnutritive Sugars Exposure

Well-being of NNS utilization during pregnancy and youth has been an issue on which various foundations either have clashing surveys or have not remarked by any means. Notwithstanding, two surveys introducing opposing perspective focuses on the long-term metabolic impacts during gestation and childhood have been found. The main survey from 2016 included examinations from early life exposure however did exclude *in utero* or breastmilk NNS presentation in light of the fact that no human investigations on this subject were accessible.[36] The subsequent study done in 2018 included two investigations of ladies devouring artificially sweetened drinks during pregnancy and lactation, which found that introduction of ASB was related to a higher danger of corpulence in contrast to no ASB exposure.[37]

Maternal Effects of Nonnutritive Sugars Exposure

There is deficient information on NNS utilization during pregnancy. No examination till date has researched maternal glucose and insulin levels or glucose resilience during pregnancy. A couple of observational investigations in grown-up human populace recommend a relationship between NNS utilization and improvement in metabolic issues;[36,38–41] however, no firm end has been drawn with respect to impact of NNS utilization on mother during pregnancy.

Offspring Effects Associated with *in utero* Nonnutritive Sugars Exposure

Birth Weight and Weight Gain

Based on discoveries in rat models, litter size was not influenced *in utero* in NNS introduction.[42] Anyway, constant NNS introduction during lactation period showed a noteworthy decrease in body weight at weaning yet not during childbirth.[31,37,42–44] Child's body weight at adulthood was likewise diminished when exposed to NNS during pregnancy and lactation.[37,45–48] A couple of studies uncovered weight gain from birth to adulthood, following *in utero* NNS exposure.[49–53] Prebirth Acesulfame-K introduction have been related to modification of child's sweet taste[47,54] inclination at high fixation yet not at ADI level.[46]

Liver Health

Liver detoxification was discovered to be less proficient in offspring of women who consumed NNS.

Gut Microbiome

There was a noteworthy increment in firmicutes, a significant gut microbial phylum, and a critical decline in *Akkermansia muciniphila* in rat offspring(s).[31] Increment in Firmicutes has been connected to weight in both mice and human.[55] A Muciniphila level is contrarily co-identified with weight gain.[56,57]

Evidence From Human Studies

Observational studies with respect to NNS introduction are however getting predominant, and information in regard to the equivalent is as yet perplexing and uncommon. The elements that have been featured to demonstrate the abovementioned explanation are many. A portion of the components depend on human cohorts including heterogeneity of tests and tests of self-announced NNS utilization. Studies done on Danish pregnant women watched a little increment in the danger of delivery and asthma in children after utilization of NNS-containing refreshments during pregnancy.[58,59] Another research done in Canada uncovered that maternal utilization of ASBs during pregnancy were related to BMI at 1-year-olds.[60] Nonetheless, a comparable report held in the United States expressed that there was no noteworthy connection between the prebirth NNS introduction and the BMI of the infant.[61]

Conclusion

Developing proof from animal studies cautions the utilization of NNS and uncovers certain impacts that weaken digestion in children. Albeit each NNS is extraordinary and can cause distinctive metabolic impacts, and scientists concede to informing the utilization regarding NNS, particularly in individuals with conditions, for example, diabetes mellitus patients, kids, and pregnant ladies. All clinical studies and research that analyze exposure to NNS during pregnancy and its long-term health impacts on mothers and babies are required to inform health associations, dietary rules, and health professionals.

References

1. Vafeiadi M, Roumeliotaki T, Myridakis A, et al. Association of early life exposure to bisphenol A with obesity and cardiometabolic traits in childhood. Environ Res 2016;146:379–387. DOI: 10.1016/j.envres.2016.01.017.
2. Vrijheid M, Casas M, Gascon M, et al. Environmental pollutants and child health-a review of recent concerns. Int J Hyg Environ Health 2016;219(4-5):331–342. DOI: 10.1016/j.ijheh.2016.05.001.
3. ACOG Committee Opinion No. 575. Exposure to toxic environmental agents. Obstet Gynecol 2013;122(4):931–935. DOI: 10.1097/01.AOG.0000435416.21944.54.
4. Gardner C, Wylie-Rosett J, Gidding SS, et al. Nonnutritive sweeteners: current use and health perspectives: a scientific statement from the american heart association and the american diabetes association. Diabetes Care 2012;35(8):1798–1808. DOI: 10.2337/dc12-9002.
5. Durán Agüero S, Angarita Dávila L, Escobar Contreras MC, et al. Noncaloric sweeteners in children: a controversial theme. Bio Med Res Int 2018;2018:4806534. DOI: 10.1155/2018/4806534.
6. Shearer J, Swithers SE. Artificial sweeteners and metabolic dysregulation: lessons learned from agriculture and the laboratory. Rev Endocr Metab Disord 2016;17(2):179–186. DOI: 10.1007/s11154-016-9372-1.
7. Sylvetsky AC, Jin Y, Clark EJ, et al. Consumption of low-calorie sweeteners among children and adults in the United States. J Acad Nutr Diet 2017;117(3):441–448.e2. DOI: 10.1016/j.jand.2016.11.004.
8. Food and Drug Administration. Additional information about high-intensity sweeteners permitted for use in food in the United States. Available at: http://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states. Accessed August 9, 2019.
9. Tellez LA, Han W, Zhang X, et al. Separate circuitries encode the hedonic and nutritional values of sugar. Nat Neurosci 2016;19(3):465–470. DOI: 10.1038/nn.4224.

10. Chandrashekar J, Hoon MA, Ryba NJP, et al. The receptors and cells for mammalian taste. Nature 2006;444(7117):288–294. DOI: 10.1038/nature05401.
11. Lee AA, Owyang C. Sugars, sweet taste receptors, and brain responses. Nutrients 2017;9(7):653. DOI: 10.3390/nu9070653.
12. Lertrit A, Srimachai S, Saetung S, et al. Effects of sucralose on insulin and glucagon-like peptide-1 secretion in healthy subjects: a randomized, double-blind, placebo-controlled trial. Nutrition 2018;55-56:125–130. DOI: 10.1016/j.nut.2018.04.001.
13. Romo-Romo A, Aguilar-Salinas CA, Brito-Córdova GX, et al. Sucralose decreases insulin sensitivity in healthy subjects: a randomized controlled trial. Am J Clin Nutr 2018;108(3):485–491. DOI: 10.1093/ajcn/nqy152.
14. Pepino MY, Tiemann CD, Patterson BW, et al. Sucralose affects glycemic and hormonal responses to an oral glucose load. Diabetes Care 2013;36(9):2530–2535. DOI: 10.2337/dc12-2221.
15. Pepino MY. Metabolic effects of non-nutritive sweeteners. Physiol Behav 2015;152:450–455. DOI: 10.1016/j.physbeh.2015.06.024##Margolskee RF, Dyer J, Kokrashvili Z, et al. T1R3 and gustducin in gut sense sugars to regulate expression of na^{+}-glucose cotransporter 1. Proc Natl Acad Sci USA 2007;104:15075–15080.
16. Jang HJ, Kokrashvili Z, Theodorakis MJ, et al. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. ProcNatl Acad Sci USA 2007;104(38):15069–15074. DOI: 10.1073/pnas.0706890104.
17. Swithers SE. Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements. Trends Endocrinol Metab 2013;24(9):431–441. DOI: 10.1016/j.tem.2013.05.005.
18. Temizkan S, Deyneli O, Yasar M, et al. Sucralose enhances GLP-1 release and lowers blood glucose in the presence of carbohydrate in healthy subjects but not in patients with type 2 diabetes. Eur J Clin Nutr 2015;69(2):162–166. DOI: 10.1038/ejcn.2014.208.
19. Simon BR, Parlee SD, Learman BS, et al. Artificial sweeteners stimulate adipogenesis and suppress lipolysis independently of sweet taste receptors. J Biol Chem 2013;288(45):32475–32489. DOI: 10.1074/jbc.M113.514034.
20. Bian X, Chi L, Gao B, et al. Gut microbiome response to sucralose and its potential role in inducing liver inflammation in mice. Front Physiol 2017;8:487. DOI: 10.3389/fphys.2017.00487.
21. Prashant GM, Patil RB, Nagaraj T, et al. The antimicrobial activity of the three commercially available intense sweeteners against common periodontal pathogens: an in vitro study. J Contemp Dent Pract 2012;13(6):749–752. DOI: 10.5005/jp-journals-10024-1222.
22. Rodearmel SJ, Wyatt HR, Stroebele N, et al. Small changes in dietary sugar and physical activity as an approach to preventing excessive weight gain: the America on the move family study. Pediatrics 2007;120(4):e869–e879. DOI: 10.1542/peds.2006-2927.
23. de Ruyter JC, Olthof MR, Seidell JC, et al. A trial of sugar-free or sugar-sweetened beverages and body weight in children. N Engl J Med 2012;367(15):1397–1406. DOI: 10.1056/NEJMoa1203034.
24. Ebbeling CB, Leidig MM, Feldman HA, et al. Effects of a low-glycemic load vs low-fat diet in obese young adults: a randomized trial. JAMA 2007;297(19):2092–2102. DOI: 10.1001/jama.297.19.2092.
25. John BA, Wood SG, Hawkins DR. The pharmacokinetics and metabolism of sucralose in the mouse. Food Chem Toxicol 2000;38(Suppl 2):S107–S110. DOI: 10.1016/S0278-6915(00)00032-6.
26. Renwick AG. The disposition of saccharin in animals and man—a review. Food Chem Toxicol 1985;23(4-5):429–435. DOI: 10.1016/0278-6915(85)90136-X.
27. Hooper NM, Hesp RJ, Tieku S. Metabolism of aspartame by human and pig intestinal microvillar peptidases. Biochem J 1994;298(3):635–639. DOI: 10.1042/bj2980635.
28. Regier DS, Greene, ed. GeneReviews® [Internet]. Seattle, WA: University of Washington; 1993-2020.
29. Koyama E, Kitazawa K, Ohori Y, et al. In vitro metabolism of the glycosidic sweeteners, stevia mixture and enzymatically modified stevia in human intestinal microflora. Food Chem Toxicol 2003;41(3):359–374. DOI: 10.1016/S0278-6915(02)00235-1.
30. Hutapea AM, Toskulkao C, Buddhasukh D, et al. Digestion of stevioside, a natural sweetener, by various digestive enzymes. J Clin Biochem Nutr 1997;23(3):177–186. DOI: 10.3164/jcbn.23.177.
31. Olivier-Van Stichelen S, Rother KI, Hanover JA. Maternal exposure to non-nutritive sweeteners impacts progeny's metabolism and microbiome. Front Microbiol 2019;10:1360. DOI: 10.3389/fmicb.2019.01360.
32. World Health Organization, Evaluation of certain food additives and contaminants: thirty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives [meeting held in Geneva from 5 to 14 June 1990]. Available at: https://apps.who.int/iris/handle/10665/40288. Accessed January 6, 2020.
33. Sweatman TW, Renwick AG. Tissue levels of saccharin in the rat during two-generation feeding studies. Toxicol Appl Pharmacol 1982;62(3):465–473. DOI: 10.1016/0041-008X(82)90147-8.
34. Sylvetsky AC, Gardner AL, Bauman V, et al. Nonnutritive sweeteners in breast milk. J Toxicol Environ Health A 2015;78(16):1029–1032. DOI: 10.1080/15287394.2015.1053646.
35. Rother KI, Sylvetsky AC, Walter PJ, et al. Pharmacokinetics of sucralose and acesulfame-potassium in breast milk following ingestion of diet soda. J Pediatr Gastroenterol Nutr 2018;66(3):466–470. DOI: 10.1097/MPG.0000000000001817.
36. Gardener H, Rundek T, Markert M, et al. Diet soft drink consumption is associated with an increased risk of vascular events in the northern manhattan study. J Gen Intern Med 2012;27(9):1120–1126. DOI: 10.1007/s11606-011-1968-2.
37. Parlee SD, Simon BR, Scheller EL, et al. Administration of saccharin to neonatal mice influences body composition of adult males and reduces body weight of females. Endocrinology 2014;155(4):1313–1326. DOI: 10.1210/en.2013-1995.
38. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the atherosclerosis risk in communities study. Circulation 2008;117(6):754–761. DOI: 10.1161/CIRCULATIONAHA.107.716159.
39. Romo-Romo A, Aguilar-Salinas CA, Brito-Córdova GX, et al. Effects of the non-nutritive sweeteners on glucose metabolism and appetite regulating hormones: systematic review of observational prospective studies and clinical trials. PLoS ONE 2016;11(8):e0161264. DOI: 10.1371/journal.pone.0161264.
40. Dhingra R, Sullivan L, Jacques PF, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation 2007;116((5):480–488. DOI: 10.1161/CIRCULATIONAHA.107.689935.
41. de Koning L, Malik VS, Rimm EB, et al. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. Am J Clin Nutr 2011;93(6):1321–1327. DOI: 10.3945/ajcn.110.007922.
42. Morahan HL, Leenaars CHC, Boakes RA, et al. Metabolic and behavioural effects of prenatal exposure to non-nutritive sweeteners: a systematic review and meta-analysis of rodent models. Physiol Behav 2020;213:112696. DOI: 10.1016/j.physbeh.2019.112696.
43. Cohen SM, Cano M, St John MK, et al. Effect of sodium saccharin on the neonatal rat bladder. Scanning Microsc 1995;9:137–147. discussion 148.
44. Curry LL, Roberts A, Brown N. Rebaudio-side A: two-generation reproductive toxicity study in rats. Food Chem Toxicol 2008;46(Suppl 7):S21–S30. DOI: 10.1016/j.fct.2008.05.005.
45. Garland EM, Shapiro R, Kraft PL, et al. Effects of in utero and postnatal sodium saccharin exposure on the nutritional status of the young rat. II. Dose response and reversibility. Food Chem Toxicol 1991;29(10):669–679. DOI: 10.1016/0278-6915(91)90124-P.
46. Choo E, Dando R. No detriment in taste response or expression in offspring of mice fed representative levels of sucrose or non-caloric sucralose while pregnant. Physiol Behav 2018;184:39–45. DOI: 10.1016/j.physbeh.2017.11.001.
47. Li WL, Chen ML, Liu SS, et al. Sweet preference modified by early experience in mice and the related molecular modulations on the peripheral pathway. J Mol Neurosci 2013;51:225–236.

48. Brunner RL, Vorhees CV, Kinney L, et al. Aspartame: assessment of developmental psychotoxicity of a new artificial sweetener. Neurobehav Toxicol 1979;1:79–86.
49. Kille JW, Ford WC, McAnulty P, et al. Sucralose: lack of effects on sperm glycolysis and reproduction in the rat. Food Chem Toxicol 2000;38(Suppl 2):S19–S29. DOI: 10.1016/S0278-6915(00)00025-9.
50. Taylor JM, Weinberger MA, Friedman L. Chronic toxicity and carcinogenicity to the urinary bladder of sodium saccharin in the in uteroexposed rat. Toxicol Appl Pharmacol 1980;54:57–75.
51. von Poser Toigo E, Huffell AP, Mota CS, et al. Metabolic and feeding behavior alterations provoked by prenatal exposure to aspartame. Appetite 2015;87:168–174.
52. Collison KS, Makhoul NJ, Zaidi MZ, et al. Interactive effects of neonatal exposure to monosodium glutamate and aspartame on glucose homeostasis. Nutr Metab (Lond) 2012;9:58.
53. Collison KS, Makhoul NJ, Zaidi MZ, et al. Gender dimorphism in aspartame-induced impairment of spatial cognition and insulin sensitivity. PLoS ONE 2012;7:e31570.
54. Zhang GH, Chen ML, Liu SS, et al. Effects of mother's dietary exposure to acesulfame-K in pregnancy or lactation on the adult offspring's sweet preference. Chem Senses 2011;36:763–770.
55. Ley RE, Bäckhed F, Turnbaugh P, et al. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA 2005;102:11070–11075.
56. Schneeberger M, Everard A, Gómez-Valadés AG, et al. Akkermansia muciniphila inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. Sci Rep 2015;5:16643.
57. Everard A, Belzer C, Geurts L, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci USA 2013;110:9066–9071.
58. Maslova E, Strøm M, Olsen SF, et al. Consumption of artificially sweetened soft drinks in pregnancy and risk of child asthma and allergic rhinitis. PLoS ONE 2013;8(2):e57261. DOI: 10.1371/journal.pone.0057261.
59. Englund-Ögge L, Brantsæter AL, Haugen M, et al. Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: a large prospective cohort study. Am J Clin Nutr 2012;96(3):552–559. DOI: 10.3945/ajcn.111.031567.
60. Azad MB, Sharma AK, de Souza RJ, et al. Association between artificially sweetened beverage consumption during pregnancy and infant body mass index. JAMA Pediatr 2016;170(7):662–670. DOI: 10.1001/jamapediatrics.2016.0301.
61. Gillman MW, Rifas-Shiman SL, Fernandez-Barres S, et al. Beverage intake during pregnancy and childhood adiposity. Pediatrics 2017;140(2):e20170031. DOI: 10.1542/peds.2017-0031.