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Artificial Sweeteners, Pregnancy, and Maternal Glucose Metabolism: A Review

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Abstract

Non-nutritive sweeteners are increasingly consumed during pregnancy through diet beverages, tabletop sweeteners, sugar-free foods, dairy products, desserts, chewing gum, and ultra-processed low-calorie products. Their use is clinically important because pregnancy is a naturally insulin-resistant state in which maternal glucose homeostasis, lipid metabolism, inflammatory tone, gut microbial ecology, and placental nutrient signaling change progressively across gestation. This review synthesizes evidence on the relationship between artificial sweetener exposure and maternal glucose tolerance, insulin sensitivity, gestational diabetes mellitus, and offspring metabolic outcomes. The available literature indicates that approved non-nutritive sweeteners generally do not acutely raise blood glucose when consumed alone and within acceptable daily intake limits. However, pregnancy-specific observational studies have reported associations between frequent or high intake of artificially sweetened products and gestational diabetes risk, insulin resistance markers, dyslipidemia, infant adiposity, and microbiome-related outcomes. Mechanistic evidence supports plausible pathways involving intestinal sweet taste receptors, incretin signaling, glucose transport regulation, gut microbiome shifts, inflammation, placental transfer, lactational exposure, and developmental metabolic programming. At present, the evidence does not prove that approved sweeteners directly cause gestational diabetes or adverse fetal metabolic outcomes, because residual confounding, reverse causality, exposure misclassification, and limited biomarker-based pregnancy trials remain major barriers. The most balanced interpretation is that occasional intake within regulatory limits is unlikely to acutely impair maternal glycemia, whereas habitual high intake during pregnancy should not be assumed metabolically neutral, especially among women with obesity, previous gestational diabetes, polycystic ovary syndrome, family history of diabetes, or other insulin-resistant phenotypes. Future research must move from broad beverage-frequency categories toward compound-specific, dose-responsive, biomarker-validated, multi-omics, and longitudinal pregnancy designs. Clinical guidance should emphasize moderation, water and unsweetened beverages as default choices, whole-food carbohydrate quality, and individualized counseling rather than routine reliance on either added sugars or artificial sweeteners.

1. Introduction

Gestational diabetes mellitus is one of the most important metabolic complications of pregnancy because it increases the risk of hypertensive disorders, cesarean delivery, fetal overgrowth, neonatal hypoglycemia, later maternal type 2 diabetes, and long-term cardiometabolic risk in the child. Recent global estimates from the International Diabetes Federation (2025) and Wang et al. (2022) show that hyperglycemia in pregnancy affects a substantial proportion of live births, with gestational diabetes forming a major component of this burden. At the same time, the modern food environment has rapidly expanded the availability of products sweetened with low- or no-calorie

sweeteners. These products are commonly marketed as diet, sugar-free, low-calorie, diabetic-friendly, or weight-conscious alternatives to sugar-containing foods and beverages, as described in recent World Health Organization guidance and U.S. Food and Drug Administration regulatory materials (World Health Organization, 2022; World Health Organization, 2023; U.S. Food and Drug Administration, 2025).

The appeal of artificial sweeteners during pregnancy is understandable. When they replace sugar-sweetened beverages or high-sugar foods, they may reduce energy intake and postprandial glucose exposure. This substitution appears especially attractive for pregnant women with excessive gestational weight gain, impaired glucose tolerance, obesity, previous gestational diabetes, or strong family history of diabetes. However, pregnancy is not simply a scaled version of non-pregnant metabolism. It is a dynamic endocrine and inflammatory condition characterized by rising insulin resistance, altered adipose tissue function, changing gut microbial ecology, increased beta-cell demand, and placental regulation of maternal-fetal nutrient flow.

The central question is therefore broader than conventional toxicological safety. Approved sweeteners may be considered safe within acceptable daily intake thresholds, but that does not automatically establish metabolic benefit or long-term neutrality during pregnancy. This review evaluates whether repeated exposure to artificial or non-nutritive sweeteners can influence maternal glucose tolerance, insulin sensitivity, gestational diabetes risk, and offspring metabolic programming. The evidence is interpreted cautiously because acute trials, pregnancy cohorts, animal models, and mechanistic studies answer different questions and do not always point in the same direction.

2. Scope and Evidence Base of the Review

This review follows a structured narrative approach informed by systematic-review principles. The main focus is on human pregnancy evidence, while adult metabolic trials, animal pregnancy models, microbiome studies, mechanistic investigations, and regulatory documents are used to interpret biological plausibility and clinical relevance. The review question is framed as follows: in pregnant individuals, how does exposure to artificial or non-nutritive sweeteners influence maternal glucose tolerance, insulin sensitivity, gestational diabetes mellitus, and related maternal or offspring metabolic outcomes?

The evidence base includes five categories of literature. The first category includes pregnancy cohort studies that evaluate artificially sweetened beverage intake, total non-nutritive sweetener intake, or biomarker-measured sweetener exposure in relation to gestational diabetes, maternal insulin resistance, infant body mass index, childhood adiposity, and microbiome outcomes (Azad et al., 2016; Zhu et al., 2017; Laforest-Lapointe et al., 2021; Plows et al., 2020; Plows et al., 2022; Liu et al., 2022; Campos et al., 2024; Huang et al., 2025). The second category includes adult randomized and crossover metabolic studies that assess acute glucose, insulin, incretin,

and oral glucose tolerance responses to specific sweeteners such as sucralose, saccharin, aspartame, or stevia (Pepino et al., 2013; Suez et al., 2014; Suez et al., 2022). The third category includes systematic reviews and meta-analyses that summarize non-sugar sweetener effects on cardiometabolic, pregnancy, and offspring outcomes (Azad et al., 2017; Toews et al., 2019; Gebremichael et al., 2024; Cai et al., 2021; Li et al., 2022; Mao et al., 2024). The fourth category includes animal and mechanistic studies that examine gut microbiota, placental transfer, inflammation, oxidative stress, and metabolic tissue function (Suez et al., 2014; Plows et al., 2020; Leth-Moller et al., 2023; Conz et al., 2023; Richardson and Frese, 2022; Del Pozo et al., 2022). The fifth category includes regulatory and public health documents, particularly those issued by the World Health Organization, the U.S. Food and Drug Administration, IARC, and JECFA (World Health Organization, 2022; World Health Organization, 2023; U.S. Food and Drug Administration, 2025; World Health Organization et al., 2023).

Because exposure definitions, outcome measures, sweetener compounds, pregnancy populations, and adjustment strategies differ widely, a pooled quantitative conclusion is not appropriate from the current evidence alone. Greater weight is placed on prospective design, pregnancy-specific outcomes, direct exposure measurement, standardized gestational diabetes diagnosis, adjustment for pre-pregnancy body mass index and diet quality, and clear separation of specific sweetener compounds. Observational associations are treated as signals requiring confirmation rather than proof of causality.

The conceptual relationship between exposure, pregnancy-specific mechanisms, and maternal-offspring outcomes is summarized in Figure 1.

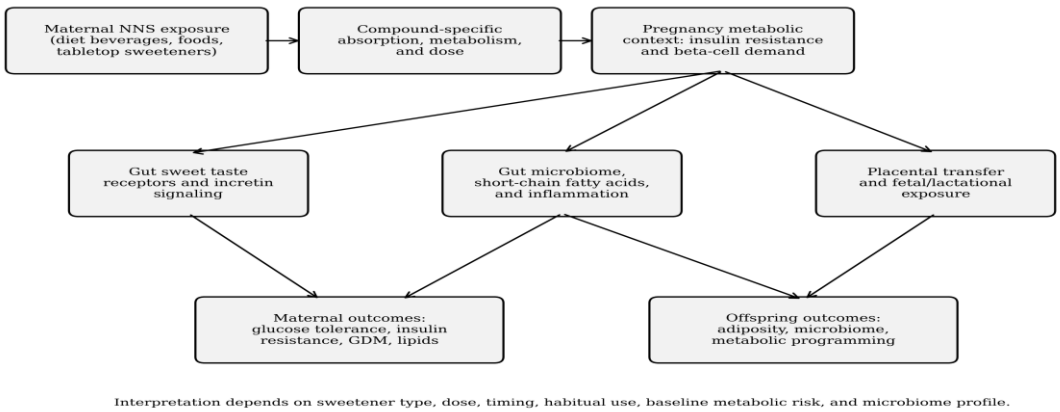

Figure 1. Conceptual flow diagram linking maternal non-nutritive sweetener exposure with metabolic pathways and maternal-offspring outcomes.

3. Concept, Classification, and Regulatory Context of Artificial Sweeteners

The terms artificial sweeteners, non-nutritive sweeteners, non-sugar sweeteners, and low/no-calorie sweeteners are often used interchangeably, but they do not refer to a single biological exposure. In this review, non-nutritive sweeteners refers to high-intensity sweetening agents that provide sweetness with little or negligible energy. Common examples include aspartame, sucralose, saccharin, acesulfame potassium, neotame, advantame, and steviol glycosides. These compounds differ in chemical structure, intestinal absorption, metabolism, excretion, placental-transfer potential, and interaction with gut nutrient-sensing pathways. Therefore, grouping all sweeteners into one exposure category can hide compound-specific effects.

Regulatory agencies usually evaluate sweeteners through toxicological frameworks based on acceptable daily intake. The U.S. Food and Drug Administration (2025) lists acceptable daily intake values for approved sweeteners, including 50 mg/kg/day for aspartame, 15 mg/kg/day for acesulfame potassium, 5 mg/kg/day for sucralose, 15 mg/kg/day for saccharin, and 4 mg/kg/day as steviol equivalents for steviol glycosides. Aspartame also requires specific attention in individuals with phenylketonuria because it is metabolized to phenylalanine, aspartate, and methanol. In 2023, IARC classified aspartame as Group 2B, while JECFA reaffirmed the acceptable daily intake, demonstrating the distinction between hazard classification and risk assessment at real-world exposure levels (World Health Organization et al., 2023).

The main approved sweeteners differ in metabolism, acceptable daily intake values, and pregnancy-relevant considerations, as summarized in Table 1.

Table 1. Selected approved artificial sweeteners and regulatory context.

Sweetener	Key features	Selected ADI	Pregnancy/metabolic considerations
Aspartame	Dipeptide methyl ester metabolized to phenylalanine, aspartate, and methanol.	FDA: 50 mg/kg/day; JECFA: 40 mg/kg/day.	Avoid in phenylketonuria. IARC classified aspartame as Group 2B in 2023, while JECFA reaffirmed the ADI.
Sucralose	Chlorinated sucrose derivative; limited absorption and largely excreted unchanged.	FDA: 5 mg/kg/day.	Human and animal studies suggest context-dependent microbiome and insulin-response effects.
Saccharin	Synthetic sulfonamide sweetener with a long history of use.	FDA: 15 mg/kg/day.	Can cross the placenta; historical rodent carcinogenicity findings are not considered directly applicable to humans at

			approved intakes.
Acesulfame potassium	Heat-stable potassium salt absorbed and excreted largely unchanged.	FDA: 15 mg/kg/day.	Reported in maternal-fetal compartments; pregnancy-specific metabolic evidence remains limited.
Steviol glycosides	Plant-derived sweeteners metabolized by gut bacteria to steviol.	FDA/JECFA basis: 4 mg/kg/day as steviol equivalents.	Often perceived as natural, but pregnancy-specific metabolic outcome evidence remains sparse.

The World Health Organization (2023) guideline on non-sugar sweeteners recommended against their use as a long-term strategy for weight control or prevention of noncommunicable diseases in the general population. Importantly, this recommendation was not a toxicological safety reassessment and did not replace acceptable-daily-intake guidance. Instead, it reflected uncertainty regarding long-term metabolic benefit and concern that observational studies sometimes show associations with cardiometabolic risk (World Health Organization, 2022). For pregnancy, this distinction is essential: regulatory safety does not equal proven metabolic benefit, and observational risk signals do not automatically prove toxicity.

4. Maternal Glucose Homeostasis During Pregnancy

Normal pregnancy requires coordinated metabolic adaptation to support fetal growth while protecting maternal energy balance. Early gestation is relatively anabolic, with increased fat storage and enhanced nutrient reserve formation. Later gestation becomes progressively insulin resistant due to placental hormones, inflammatory mediators, adipokine changes, lipolysis, and altered hepatic and skeletal muscle insulin sensitivity. In healthy pregnancy, pancreatic beta-cells compensate through increased insulin secretion. Gestational diabetes develops when beta-cell compensation is insufficient for the degree of insulin resistance.

This physiological background explains why evidence from non-pregnant adults must be applied cautiously. A sweetener that produces no measurable acute glycemic response in a healthy non-pregnant adult may behave differently in late pregnancy, when insulin secretion, incretin signaling, intestinal nutrient absorption, lipid flux, and inflammatory tone are already altered. Moreover, women with obesity, polycystic ovary syndrome, prior gestational diabetes, or early pregnancy dysglycemia may enter pregnancy with reduced metabolic reserve. In such individuals, subtle diet-microbiome or incretin effects could become more clinically meaningful.

The most relevant maternal metabolic outcomes include fasting glucose, postprandial glucose, oral glucose tolerance test values, fasting insulin, HOMA-IR, insulin sensitivity indices, lipid traits, inflammatory markers, gestational weight gain, and the clinical diagnosis of gestational diabetes mellitus. However, each

marker has limitations. HbA1c can be affected by hemodilution, iron status, and altered red cell turnover during pregnancy. HOMA-IR is convenient but does not fully capture pregnancy-specific insulin dynamics. Clamp-based insulin sensitivity studies would provide stronger evidence, but pregnancy-specific sweetener studies using this method are essentially absent.

5. Human Evidence on Glucose Tolerance, Insulin Sensitivity, and Gestational Diabetes

Most controlled metabolic trials have been conducted in non-pregnant adults. In general, artificial sweeteners consumed alone do not consistently raise plasma glucose, which supports their short-term glycemic neutrality under controlled conditions. However, this does not mean that all sweeteners are metabolically inert in all settings. Pepino et al. (2013) reported that sucralose altered glucose and insulin responses to an oral glucose load in obese adults who were not habitual consumers of non-nutritive sweeteners. Suez et al. (2022) later showed that saccharin and sucralose, at doses below acceptable daily intake, impaired glycemic responses in some individuals and produced microbiome changes that could transfer metabolic features to germ-free mouse models. These studies support a responder framework in which baseline microbiome composition, habitual use, obesity, and metabolic phenotype may influence sweetener response.

Pregnancy-specific human evidence is mainly observational. This is a major limitation because individuals at higher risk of gestational diabetes may choose diet products because they are already concerned about weight or glucose. This creates reverse causality. Artificially sweetened beverage intake also correlates with pre-pregnancy body mass index, diet quality, smoking, socioeconomic status, physical activity, and health-seeking behavior. Even after statistical adjustment, residual confounding may remain. Nevertheless, several pregnancy studies provide important signals that deserve careful interpretation.

In the Canadian CHILD cohort, Azad et al. (2016) reported that daily maternal consumption of artificially sweetened beverages was associated with higher infant body mass index z-score and increased odds of overweight at one year. In the Danish National Birth Cohort, among pregnancies affected by gestational diabetes, Zhu et al. (2017) found that maternal artificially sweetened beverage intake was associated with offspring birth size and later overweight or obesity through seven years of age. These studies do not directly prove maternal glucose impairment, but they suggest that prenatal sweetener exposure may be linked to offspring metabolic trajectory.

More direct maternal metabolic evidence has emerged from biomarker and cohort studies. Liu et al. (2022) measured serum aspartame and sucralose in pregnant women and found detectable fasting levels. Serum levels did not clearly distinguish women with and without gestational diabetes, but higher aspartame concentrations were associated with insulin resistance and adverse lipid traits after adjustment. Campos

et al. (2024) reported that non-nutritive sweetener consumption, particularly sucralose, was associated with increased gestational diabetes risk in a Chilean pregnancy cohort. Huang et al. (2025) similarly reported in a Chinese cohort analysis that high consumption of sucralose, aspartame, and sodium saccharin was linked with higher gestational diabetes incidence. These results are clinically relevant, but causality remains unproven.

Selected human studies that shape the current interpretation of maternal and offspring metabolic outcomes are summarized in Table 2.

Table 2. Selected human evidence relevant to maternal glucose metabolism and pregnancy outcomes.

Study	Design/sample	Exposure	Outcome	Main interpretation
Pepino et al. (2013)	Crossover trial; 17 obese adults.	Sucralose before oral glucose tolerance testing.	Glucose and insulin response.	Sucralose altered glycemic and hormonal responses to oral glucose in non-habitual users.
Suez et al. (2022)	Randomized trial; 120 healthy adults.	Saccharin, sucralose, aspartame, and stevia compared with controls.	Glycemic response and microbiome.	Saccharin and sucralose impaired glycemic responses in some participants, supporting microbiome-mediated variability.
Azad et al. (2016)	Prospective pregnancy cohort; CHILD study.	Artificially sweetened beverage intake during pregnancy.	Infant BMI at one year.	Daily intake was associated with higher infant BMI z-score and increased odds of overweight.
Zhu et al. (2017)	Prospective cohort; 918 GDM mother-child dyads.	Artificially sweetened beverage intake during pregnancy.	Offspring growth to seven years.	Positive associations were reported with birth size and later overweight or obesity.
Liu et al. (2022)	Nested case-control study; 218 pregnant women.	Serum aspartame and sucralose.	GDM, HOMA-IR, and lipid traits.	No clear exposure difference by GDM status; higher aspartame was associated with insulin resistance and dyslipidemia.
Campos et al. (2024)	Secondary cohort analysis; 1,472 pregnant women.	NNS intake, with sucralose emphasized.	GDM incidence.	NNS consumption, especially sucralose, was associated with increased

				GDM risk.

6. Evidence from Systematic Reviews and Adult Metabolic Trials

Systematic reviews help place individual studies into perspective. Azad et al. (2017) and Toews et al. (2019) found that short-term randomized trials in general adult populations often show modest weight or energy-intake benefits when sweeteners replace sugar, whereas long-term observational studies sometimes show associations with cardiometabolic outcomes. This pattern partly explains why public health recommendations are cautious: short-term substitution effects do not necessarily translate into long-term metabolic benefit.

Pregnancy-focused systematic reviews reach similarly careful conclusions. Reviews evaluating perinatal consumption of low-calorie sweeteners have reported possible associations with maternal outcomes such as gestational diabetes, preterm birth, and offspring adiposity, but the certainty of evidence remains limited because most studies are observational and heterogeneous (Gebremichael et al., 2024; Cai et al., 2021; Li et al., 2022; Mao et al., 2024). These reviews consistently emphasize the lack of long-term randomized trials in pregnant populations, the scarcity of biomarker-based exposure assessment, and the need to separate sweetener type rather than treating all compounds as equivalent.

The apparent contradiction between controlled trials and pregnancy cohorts can be understood by recognizing that they answer different questions. Acute trials ask whether a sweetener causes immediate glucose elevation under controlled conditions. Pregnancy cohorts ask whether habitual intake patterns over weeks or months are associated with maternal and offspring outcomes. A sweetener may not acutely raise glucose when consumed alone yet may still be linked with outcomes through diet patterning, microbiome response, co-ingested carbohydrates, compensatory eating, or baseline metabolic risk. Therefore, both lines of evidence should be integrated rather than treated as mutually exclusive.

7. Mechanistic Targets: Sweet Taste Receptors, Incretins, and Glucose Transport

One mechanistic pathway involves sweet taste receptors. T1R2/T1R3 receptors are not confined to the tongue; they are also expressed in intestinal enteroendocrine and nutrient-sensing systems. Activation of these receptors may influence glucose transporter regulation, incretin hormone release, intestinal glucose absorption, gastric emptying, and cephalic-phase insulin responses. The clinical magnitude of these effects in humans remains debated because responses vary by sweetener compound, dose, timing, habitual exposure, and whether carbohydrate is consumed at the same time.

Incretin signaling is particularly relevant to pregnancy because maternal beta-cells already face increased secretory demand. GLP-1 and GIP support glucose-dependent insulin secretion after meals. Some experimental studies suggest that sucralose or other sweeteners may alter GLP-1 release

under specific conditions, whereas other studies show little or no meaningful effect. The difference may depend on whether the sweetener is consumed alone, before a glucose load, or as part of a mixed meal. The metabolic phenotype of the participant also matters: lean, insulin-sensitive, obese, insulin-resistant, and pregnant individuals should not be assumed to respond identically.

Another possible pathway involves glucose transporter regulation. If sweetener exposure changes intestinal glucose uptake or transporter expression in the presence of carbohydrate, the postprandial glycemic response could change even though the sweetener itself supplies little energy. At present, this pathway is biologically plausible but not adequately proven in pregnant humans. Future studies should combine controlled feeding, continuous glucose monitoring, incretin assays, and compound-specific exposure measurement to determine whether intestinal nutrient-sensing effects are clinically important during gestation.

8. Gut Microbiome, Inflammation, and Host-Metabolic Variability

The gut microbiome is one of the most important proposed bridges between artificial sweeteners and glucose metabolism. Suez et al. (2014) reported that artificial sweeteners could induce glucose intolerance through microbiome alterations in mice and in a subset of humans. Their later randomized human trial strengthened the concept of individualized response, showing that saccharin and sucralose altered glycemic responses in some participants and that microbiome features contributed to this variability (Suez et al., 2022). Reviews by Conz et al. (2023), Richardson and Frese (2022), and Del Pozo et al. (2022) conclude that microbiome effects differ by compound and that human findings are not fully consistent, but the hypothesis remains biologically credible.

Pregnancy adds a unique layer to this mechanism. The maternal gut microbiome naturally shifts across gestation, and these changes may increase energy harvest, inflammatory tone, and insulin resistance. Artificial sweetener exposure during this period could theoretically amplify dysbiosis, alter short-chain fatty acid production, increase gut permeability, or promote metabolic endotoxemia. These effects could worsen hepatic and adipose tissue insulin resistance in susceptible individuals. However, this complete pathway has not yet been directly demonstrated in pregnant humans, so it should be described as plausible rather than established.

Inflammation and oxidative stress also require attention. Late pregnancy already involves low-grade inflammation, and excessive inflammatory activation contributes to gestational insulin resistance. Plows et al. (2020) suggested in an animal pregnancy model that sweetener exposure can affect adipose tissue function, glucose tolerance, inflammatory markers, and oxidative stress, but doses, exposure matrices, and species differences limit direct translation to human pregnancy. Animal findings are therefore best used to generate mechanisms and guide human study design, not to make direct clinical risk estimates.

9. Placental Transfer, Lactation, and Offspring Programming

A defining feature of pregnancy exposure is the possibility of fetal contact. Leth-Moller et al. (2023) reported that selected sweeteners, including acesulfame, cyclamate, saccharin, and sucralose, can cross the placental barrier and reach fetal-side compartments. This finding does not prove harm, but it shows that fetal exposure is biologically possible. Sweeteners or their metabolites have also been discussed in relation to lactational exposure, colostrum microbiota, and early-life microbial development (Concha et al., 2023; Tapia-González et al., 2023).

The developmental origins of health and disease framework provides a useful model for interpreting offspring findings. Prenatal dietary exposures may influence long-term metabolic risk through placental nutrient transport, fetal appetite regulation, adipocyte development, microbial seeding, epigenetic programming, and postnatal feeding behavior. Human evidence directly linking artificial sweeteners to fetal epigenetic changes remains limited. However, associations with infant body mass index, childhood adiposity, infant microbiota, and metabolic modifications support continued investigation (Azad et al., 2016; Zhu et al., 2017; Laforest-Lapointe et al., 2021; Plows et al., 2022; Li et al., 2022).

The principal mechanistic pathways proposed in the literature are organized in Table 3.

Table 3. Mechanistic pathways linking artificial sweetener exposure to maternal glucose tolerance and fetal metabolic programming.

Pathway	Mechanistic hypothesis	Evidence status
Sweet taste receptor signaling	T1R2/T1R3 activation in oral and intestinal tissues may modulate glucose transport and incretin secretion.	Moderate biological plausibility; human effect sizes remain uncertain.
Incretin modulation	Potential GLP-1 and GIP changes could affect insulin secretion after carbohydrate exposure.	Mixed evidence; effects appear context dependent.
Gut microbiome	NNS may alter microbial composition, microbial function, short-chain fatty acids, and glycemic responses.	Strong mechanistic interest; personalized effects are likely.
Inflammation and oxidative stress	Dysbiosis and metabolic endotoxemia may promote inflammatory pathways and worsen insulin resistance.	Evidence is mainly from animal models and indirect human studies.
Placental transfer	Selected sweeteners may cross the placenta, allowing fetal exposure.	Demonstrated for selected compounds; clinical outcome relevance is uncertain.

Fetal programming	Prenatal exposure may influence appetite, adiposity, microbiome development, and later insulin sensitivity.	Suggestive observational evidence; causal pathways remain unproven.

Offspring adiposity is currently one of the most consistent pregnancy-related signals. Azad et al. (2016) reported higher infant BMI z-score and higher odds of overweight at one year with daily maternal artificially sweetened beverage intake. Zhu et al. (2017) reported associations with offspring growth and adiposity through seven years among pregnancies affected by gestational diabetes. Laforest-Lapointe et al. (2021) found that maternal artificially sweetened beverage consumption was associated with infant gut microbiota and metabolic modifications as well as increased infant BMI. These findings cannot establish causality, but they show why pregnancy exposure should not be dismissed as irrelevant to long-term metabolic health.

10. Clinical and Public Health Implications

The most useful clinical message is balanced moderation. Current evidence does not support alarmist claims that approved sweeteners are universally harmful when consumed occasionally within acceptable daily intake limits. At the same time, the evidence does not support promoting frequent diet beverage or sugar-free ultra-processed product intake as a proven strategy to prevent gestational diabetes or improve offspring metabolic health. The safest clinical interpretation is that artificial sweeteners may be preferable to high sugar intake in selected substitution contexts, but water, unsweetened beverages, and high-quality whole-food dietary patterns remain better default options.

Counseling should be individualized according to metabolic risk. For a pregnant woman who consumes large amounts of sugar-sweetened beverages, partial replacement with non-nutritive sweetened beverages may reduce sugar exposure in the short term. However, the longer-term goal should be gradual reduction in sweetness dependence and transition toward water, unsweetened milk where appropriate, unsweetened tea, and balanced meals rich in fiber and minimally processed carbohydrates. For women with obesity, previous gestational diabetes, polycystic ovary syndrome, abnormal early pregnancy glucose, or strong family history of diabetes, clinicians may reasonably advise minimizing habitual high intake of artificially sweetened products.

Public health communication must avoid two errors. The first error is to equate regulatory approval with proven metabolic advantage. Acceptable daily intake thresholds indicate toxicological safety at specified exposure levels; they do not prove benefit for maternal insulin sensitivity or fetal metabolic programming. The second error is to treat observational associations as proof of toxicity. A responsible message is that occasional use within approved limits is unlikely to cause acute glycemic harm, but chronic high intake should not be

encouraged as a health-promoting pregnancy behavior.

11. Challenges and Trade-Offs in Interpretation

The first major challenge is exposure misclassification. Many studies measure diet beverage frequency rather than actual milligrams of aspartame, sucralose, saccharin, acesulfame potassium, or steviol glycosides. This is problematic because modern sweeteners appear in beverages, yogurts, desserts, protein products, medications, supplements, and tabletop mixtures. Consumers may not know which sweetener they are consuming, and product formulations may change over time. Biomarker-based exposure assessment is therefore essential for stronger evidence.

The second challenge is compound grouping. Different sweeteners have different absorption, metabolism, excretion, placental transfer, and microbiome effects. Aspartame is metabolized into amino acids and methanol; sucralose is largely excreted unchanged but may interact with the gut microbiome; saccharin and acesulfame potassium can be absorbed and excreted in different patterns; steviol glycosides depend on gut bacterial metabolism. A combined non-nutritive sweetener variable may therefore conceal risk signals for one compound and null effects for another.

The third challenge is confounding and reverse causality. Pregnant women at higher risk of gestational diabetes may switch to diet products because of clinical advice, self-concern, or early metabolic symptoms. Such individuals may already differ in body mass index, diet quality, physical activity, socioeconomic status, family history, and medical surveillance. Even sophisticated statistical adjustment cannot fully remove this problem. Therefore, observed associations should be interpreted as potential risk signals rather than definitive causal relationships.

The fourth challenge is outcome heterogeneity. Studies use different gestational diabetes diagnostic criteria, exposure windows, dietary questionnaires, follow-up ages, and infant growth measures. Some focus on maternal glucose, others on offspring adiposity, microbiome composition, preterm birth, or hypertensive disorders. These differences make direct comparison difficult. The field requires harmonized exposure definitions, trimester-specific timing, standardized glucose outcomes, and long-term offspring follow-up.

Across the major outcome domains, the certainty of evidence remains uneven; this is summarized in Table 4.

Table 4. Evidence certainty and interpretation across major outcome domains.

Outcome/domain	Evidence certainty	Interpretation
Acute fasting glucose response	Moderate to high	Most trials show little effect when NNS are consumed alone; evidence is not pregnancy-specific.

Insulin response with carbohydrate co-ingestion	Moderate	Some sucralose and microbiome studies show context-specific effects.
Maternal GDM risk	Low to moderate	Observational associations are emerging, but confounding and reverse causality remain major limitations.
Pregnancy insulin sensitivity indices	Low	Few studies are available, biomarker data are limited, and large clamp studies are absent.
Offspring adiposity	Moderate observational	Several cohorts suggest positive associations; causal mechanisms remain unproven.
Microbiome-mediated effects	Moderate mechanistic	Biological plausibility is strong, but pregnancy-specific pathway evidence is incomplete.
Placental/fetal exposure	Moderate for selected compounds	Transport has been demonstrated for selected compounds; clinical outcome significance is uncertain.

12. Future Research Framework

The next generation of research should begin before pregnancy or in early gestation and follow mothers and infants through lactation and childhood. Pragmatic randomized trials are needed to compare water or unsweetened beverage substitution, non-nutritive sweetener substitution, and sugar-sweetened beverage reduction in populations with different baseline metabolic risk. Important endpoints should include oral glucose tolerance test results, continuous glucose monitoring metrics, fasting insulin, insulin sensitivity indices, gestational weight gain, lipid profiles, inflammatory markers, maternal microbiome, placental biomarkers, and offspring growth.

Biomarker-based exposure assessment is a core requirement. Serum, urine, amniotic fluid, cord blood, placenta, breast milk, and infant samples can help distinguish reported intake from actual internal exposure. Future studies should measure individual compounds and metabolites rather than relying only on food-frequency questionnaires. This is especially important because many products contain blends of sweeteners and because label literacy varies across populations.

Multi-omics studies can clarify mechanism. An ideal design would combine dietary records, sweetener biomarkers, metagenomics, metabolomics, bile acid profiling, inflammatory markers, placental transporter expression, epigenomics, and longitudinal infant microbiome data. Such designs could identify responder phenotypes and determine whether sweetener exposure is a causal contributor, a marker of unhealthy dietary patterns, or both. They

may also clarify whether women with obesity, prior gestational diabetes, or polycystic ovary syndrome are more susceptible to metabolic effects.

Research must also address public health relevance. The practical question is not whether a single sweetener dose changes glucose during a laboratory test, but whether real-world patterns of sweetener use improve or worsen maternal and offspring metabolic health compared with realistic alternatives. Comparators should include water, unsweetened beverages, sugar-sweetened beverages, and broader dietary improvement. Without such comparator clarity, clinical recommendations will remain uncertain.

Priority questions for future pregnancy research are summarized in Table 5.

Table 5. Research priorities for future pregnancy studies on non-nutritive sweeteners.

Priority area	Core question	Recommended design
Randomized trials in high-risk pregnancy	Does replacing sugar-sweetened beverages with NNS beverages versus water affect GDM and insulin sensitivity?	Randomized substitution trial with continuous glucose monitoring and OGTT endpoints.
Biomarker validation	How accurately do food-frequency questionnaires capture sweetener exposure?	Paired food-frequency questionnaire, dietary-record, and serum or urinary biomarker panels.
Placental transfer	Which sweeteners reach fetal circulation and at what concentrations?	Maternal blood, cord blood, placenta perfusion, and amniotic-fluid studies.
Microbiome responders	Which baseline microbiome patterns predict glucose response to NNS?	Longitudinal metagenomics and metabolomics in pregnancy.
Offspring follow-up	Do prenatal exposures influence adiposity, insulin sensitivity, or appetite beyond early childhood?	Prospective cohorts with follow-up into adolescence.

13. Conclusion

Artificial sweeteners occupy a complex position in pregnancy nutrition. They can reduce sugar and energy exposure when used as substitutes for sugar-sweetened products, and approved compounds are regulated using acceptable-daily-intake thresholds intended to protect against toxicological risk. However, pregnancy-specific metabolic neutrality has not been conclusively established. Acute studies generally show little immediate glycemic effect when sweeteners are consumed alone, yet observational pregnancy studies and mechanistic research raise credible concerns

about habitual high intake, particularly among individuals with insulin-resistant phenotypes.

The most defensible conclusion is that approved artificial sweeteners are unlikely to acutely and directly impair maternal glucose metabolism at occasional intakes within approved limits, but frequent high consumption during pregnancy should not be assumed metabolically harmless. The field requires compound-specific, biomarker-validated, longitudinal, and pregnancy-focused research before stronger causal conclusions can be made. Until such evidence is available, clinicians should recommend moderation, prioritize water and unsweetened beverages, support whole-food carbohydrate quality, and individualize guidance for pregnant individuals at elevated risk of gestational diabetes or metabolic disease.

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