NASEM Webinar: Assessing Human Requirements for Carbohydrate

# Role and Requirements of Carbohydrate in Pregnancy, Lactation, and Infancy

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## Context of Gestational Weight Gain


| Weight category | Prepregnancy BMI (kg/m²) | Total GWG recommendation |
|---|---|---|
| Underweight | <18.5 | 12.5-18 kg<br>28-40 lb |
| Normal weight | 18.5-24.9 | 11.5-16 kg<br>25-35 lb |
| Overweight | 25-29.9 | 7-11.5 kg<br>15-25 lb |
| Obese* | > or = 30 | 5-9 kg<br>11-20 lb |

*Not enough evidence available to make recommendations for higher obesity classifications.

IOM (Institute of Medicine) and NRC (National Research Council). *Weight Gain During Pregnancy: Reexamining the Guidelines*. 2009. Washington, DC: The National Academies Press.

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# Carbohydrates During Pregnancy

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## Pregnancy Carbohydrate DRIs


- Increased fuel requirement
  - Increased metabolic rate
  - Establishment of placental-fetal unit
  - Growth and development of fetus
  - Increased energy stores (especially early/mid pregnancy)
  - Increased energy expenditure (especially late pregnancy)
- Fetus utilizes glucose for energy, can use ketones

Institute of Medicine. DRIs. Washington, DC: The National Academies Press, 2005.

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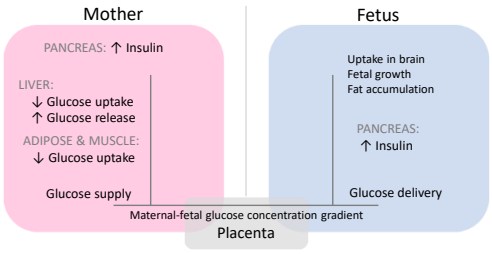
## Normal CHO metabolism in late pregnancy

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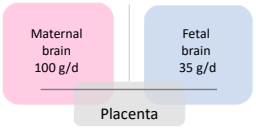
## Pregnancy Carbohydrate DRIs

| | Basis | EAR | RDA |
|---|---|---|---|
| **Non-pregnant females** | Brain's requirement for glucose | 100 g/d | 130 g/d |
| **Pregnant females** | EAR for non-pregnant + 35 g/d for fetal brain | 135 g/d | 175 g/d |

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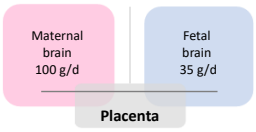
## Pregnancy CHO requirement – the Placenta

- Placenta prefers glucose
- High expression of glucose transporters
- Current DRIs underestimate CHO need
- *In vivo* studies:
  - Of uteroplacental glucose uptake:
    - Fetus accounts for 70% of glucose consumption
    - Placenta accounts for 30% of glucose consumption
  - **Placenta glucose consumption calculated at 36 g/d**

EAR accounting for placental CHO: 100g + 35g + 36g = 171 g/d




Hernandez TL, Rozance PJ. *Am J Clin Nutr*. 2023;117(2):227-234.
Michelsen TM, et al. *J Clin Endocrinol Metab*. 2019.

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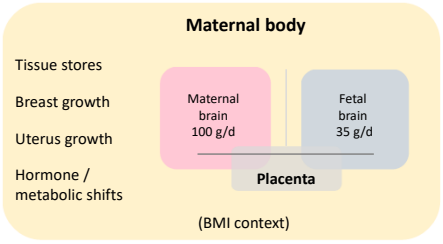
## Pregnancy CHO requirement – the Big Picture




A pregnant body is not simply a non-pregnant body with a placenta and a fetus.

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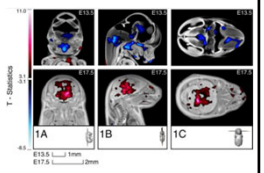
## Ketogenic diet during pregnancy: Rodent models

- Adverse effects in mothers
  - Reduced fertility
  - Reduced litter size
  - High risk of fatal ketoacidosis during lactation
- Adverse fetal effects reported
  - Fetal overgrowth followed by slowed growth
  - Changes in brain structures – smaller overall size
  - Susceptibility to depression/anxiety
  - Changes in organ size
  - Slow growth after birth

Sussman D, et al. *BMC Pregnancy Childbirth*. 2013;13:198
Sussman D, et al. *BMC Pregnancy Childbirth*. 2013;13:109
Sussman D, et al. *Brain Behav*. 2015;5(2):e00300




Brain regions that are statistically different in the ketogenic diet compared with standard diet embryos.
Blue regions = significantly smaller in KD.
Red regions = significantly larger in KD.
Sussman et al. 2013;13:109.

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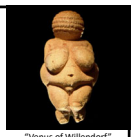
## Low CHO before pregnancy: Fertility


"Venus of Willendorf"

- Excess weight is a risk factor for infertility
- Weight loss improves fertility
- Systematic review of 7 studies examining diets providing total energy as <45% CHO vs usual diet (with or without energy restriction)
  - Reduced circulating insulin
  - Resumed ovulation
  - Improved pregnancy rates
- Unclear whether CHO restriction or energy restriction most impactful
- Minimal research on low CHO in overweight without PCOS

McGrice & Porter. *Nutrients*. 2017;9(3).

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## Low CHO before pregnancy: The National Birth Defects Prevention Study

- Association between CHO and neural tube defects (1998-2011)
- n=1740 mothers with NTD; n=9545 controls
- Defined *restricted CHO* as ≤5th percentile among controls (95 g/d)
- *Restricted CHO* diet 30% increased adjusted odds of neural tube defect [AOR 1.3 (1.02-1.67)]

| Intake | Restricted CHO (n=479) | Non-restricted CHO (n=9064) | *P*-value |
|---|---|---|---|
| **Dietary folate equivalent** | 217.9 DFE | 540.1 DFE | <0.01 |
| **Folic acid supplement** | 31.1% daily<br>63.5% none | 30.9% daily<br>64.1% none | 0.21 |
| **Intended pregnancy** | 53.7% | 47.5% | <0.05 |

Desrosiers et al. *Birth Defects Res*. 2018.
Shaw GM, Yang W. *Birth Defects Res*. 2019.

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## Maternal CHO in Pregnancy & Infant Outcome

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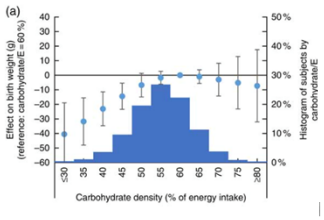
## CHO intake in pregnancy and birth weight

- Japanese cohort (2011-2014)
- N=91,637 (excluded GDM)
- Mean CHO intake:
  - 234 (77) g/d CHO at 20-28wk
  - 55.3% energy intake
- Low CHO threshold 45% energy

"Results strongly suggest that a balanced diet fulfilling minimum requirement for all macronutrients was ideal for avoiding fetal growth restriction."




Association between dietary CHO density and birth weight

Morisaki N, et al. *Br J Nutr.* 2018;120(12):1432-40.

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## Low CHO during pregnancy – infant outcomes: Key findings

- Lower birth weight and fat mass associated with *low CHO* intake
- Smaller head circumference with severe *CHO restriction* (~100 g/d) and *modestly low CHO* (135 vs 200 g/d)
- Length at birth lower with lower CHO intake
- Results confounded by energy intake!

1) Sweeting A, et al. *Nutrients.* 2021; 2) Morisaki et al. *Br J Nutr.* 2018; 3) Fahey CA, et al. *PLoS ONE.* 2019; 4) Harreiter J, et al. *Diabetes Care* 2019; 5) Eshak ES, et al. *Br J Nutr.* 2020; 6) Renault KM, et al. *Am J Clin Nutr* 2015;102:1475-81. 7) Powell CD, et al. PLoS ONE. 2020; 8) Mijatovic J, et al. *Am J Clin Nutr.* 2020; 9) Tanner H, et al. *Nutrients.* 2021;13(10).

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## Carbohydrates During Lactation

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## Lactation Carbohydrate DRIs


- CHO requirements increase for lactating woman
- Human milk contains ~74 g/L lactose
  - Caloric requirement of lactose = 240 kcal/d (0.78 L/d)
  - Lactose synthesized from glucose
  - Increased supply required (ingested CHO or protein)
  - Lactose concentrations have remarkably little variation (2-4%)

Institute of Medicine. DRIs. 2005.
Nommsen et al. *Am J Clin Nutr* 1991;53:457-65.

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## Lactation Carbohydrate DRIs

| | Basis | EAR | RDA |
|---|---|---|---|
| Non-pregnant females | Brain's requirement for glucose | 100 g/d | 130 g/d |
| Pregnant females | EAR for non-pregnant + 35 g/d for fetal brain | 135 g/d | 175 g/d |
| Lactating females | EAR for non-pregnant + 60 g/d for lactose in milk* | 160 g/d | 210 g/d |

*Assumes lactose concentration 74 g/dL
And daily volume production of 0.78 L/d

Institute of Medicine. DRIs. 2005.

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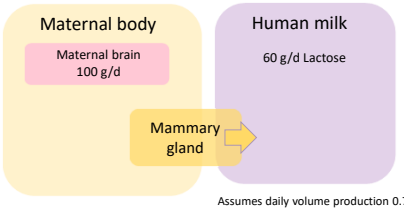
## Lactation CHO requirement




Assumes daily volume production 0.78 L/d

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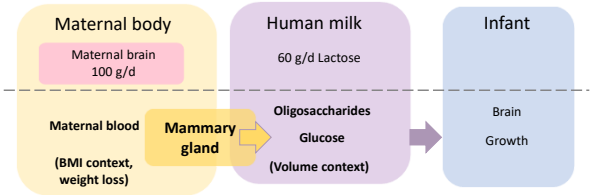
## Lactation CHO requirement – the Big Picture




Assumes daily volume production 0.78 L/d

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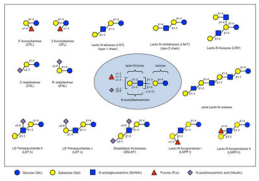
## CHO components in human milk

- Producing human milk requires substantial CHO substrate
- Lactose
  - Primary CHO in human milk: 74 g/dL
  - 74 g/L x 0.78 L/d = **60 g/d**
- Oligosaccharides
  - 3rd largest component in human milk: 1-1.5 g/dL
  - 1.0 to 1.5 g/dL x 0.78 L/d = **8 to 12 g/d**
  - Important health impact on infant
- Glucose and/or fructose
  - Small amounts
  - Unclear impact



Triantis V, et al. Immunological Effects of Human Milk Oligosaccharides. *Frontiers in Pediatrics*. 2018;6.

Bode L. *Early Hum Dev*. 2015;91(11):619-22

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## Lactation ketoacidosis – rare condition

- 18 case reports on 19 patients (1982 to 2022)
- Presenting symptoms: nausea, vomiting, malaise, abd pain, dyspnea
- Ketonemia or ketonuria and anion gap metabolic acidosis
- Precipitating factors:
  - Low CHO, high protein, ketogenic, or low calorie diet
  - Decreased intake for other reasons

Full recovery achieved with IV Dextrose + "CHO-rich" or a "balanced diet".

Al Alawi et al. *Medicina*. 2020;56(6).
Osborne KC, Oliver JJ. *Am J Emerg Med*. 2022;56:392.e5-.e6.

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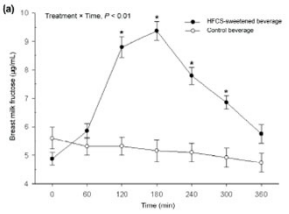
## Non-lactose CHO in human milk

- Small amount of glucose and fructose
- Modified by consumption of high-fructose corn syrup sweetened beverage
- Fructose increase sustained for 5 hours, but in small quantities (mcg/mL)
- Fructose consumption and concentration in milk are linked
- Possible metabolic effect in infant




Breast milk concentrations of fructose of 41 women after consumption of HFCS-sweetened beverage or control beverage. Values are mean ± standard error.

Berger PK, et al. *Nutrients*. 2018;10(6):669.

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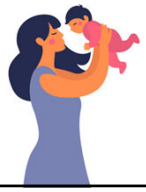
## Carbohydrates During Infancy



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## Infancy Carbohydrate DRI


"The lower limit for dietary carbohydrate compatible with life or for optimal health in infants is unknown."

- Human milk = optimal source of infant nutrition
- Lactose = glucose + galactose

Institute of Medicine. DRIs. 2005.
Gidrewics & Fenton. *BMC Pediatrics*. 2014;14:216.

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## Infancy Carbohydrate DRIs

| Infant Age | Basis | Adequate Intake |
|---|---|---|
| 0-6 months | 0.78 L/d human milk x 74 g/L = 60g | 60 g/d |
| 7-12 months | 0.6 L/d human milk x 74 g/L = 44g<br>+<br>Median carbohydrate intake from complementary foods from 3rd NHANES = 51g | 95 g/d |

Institute of Medicine. DRIs. 2005.

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## CHO in infant formulas

| Formula | CHO type |
|---|---|
| Enfamil Enspire | **Lactose** |
| Good Start Gentle | **Lactose, corn malto-dextrin** |
| Similac Pro-Advance | **Lactose** |
| Similac for Supplementation | **Lactose** |
| Pure Bliss by Similac | **Lactose** |
| Enfamil A.R. | **Rice starch, lactose, maltodextrin** |
| Enfamil Gentlease | **Corn syrup solids** |
| Good Start Soothe | **Corn maltodextrin** |
| Similac Pro-Sensitive | **Corn syrup, sugar** |

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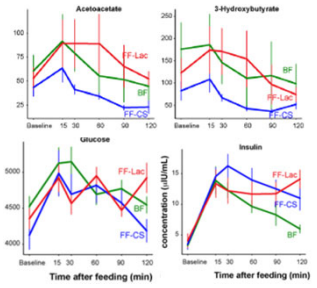
## Postprandial response to CHO sources

- RCT of formula-fed infants (n=30)
  - Lactose formula
  - Corn syrup solids (CSS) formula
  - Breastfed infants
- Ketones lower with CSS formula
- Insulin higher with CSS formula
- Metabolic differences apparent




Slupsky CM, et al. *Sci Rep*. 2017;7(1):3640.

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## CHO during Pregnancy, Lactation and Infancy:

Summarizing the research

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## Challenges

- Maternal glucose concentrations not reported
- Estimation of CHO intake and timing of intake
- Definition of "low carbohydrate" and "carbohydrate restriction" varies
- CHO intake confounded by total energy intake
- Change in CHO results in changes in fat and protein intake

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## Gaps in knowledge – The Unknown

**Unknown:**

- CHO needs of pregnant body (aside from brain)
- CHO needs of lactating body (aside from brain)
- CHO needs based on BMI – overweight/obese vs. normal weight
- CHO needed to produce all human milk CHO
- CHO requirement for non-exclusively breastfeeding mother
- CHO across the lifecycle by racial/ethnic groups
- Range of acceptable macronutrient distribution
  - Lower end for infants
  - Upper end for all
- Impact of alternative CHO sources on infant outcomes and long-term health
- Optimal CHO content of complementary foods unknown

MUCH REMAINS UNKNOWN!

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## Summary

- CHO during pregnancy is important for normal fetal growth and development
- CHO needs for conception and pregnancy may differ by BMI status
- CHO requirements are high for production of human milk – not all of which are accounted for in current DRIs
- Exclusively breastfed infants have best outcomes
- Alternative CHO sources in infant formula require more investigation and should more closely mimic breast milk
- Range of acceptable CHO intake remains unknown

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## Thank you! …… Questions?

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## Usual Intakes in pregnant women
(NHANES 2001-2014)

| Dietary component | EAR for pregnancy | Mean intake from foods | Foods + supplements* | % <EAR |
|---|---|---|---|---|
| Energy, kcal/d | - | 2232 | n/a | n/a |
| Carbohydrate, g/d | - | 294 (51% energy) | n/a | n/a |
| Thiamin, mg/d | 1.2 | 1.8 | 3.6 mg/d | 5.7% |
| Folate, mcg DFE/d | 520 | 630 | 1451 mcg DFE/d | 16.4% |
| Iron, mg/d | 22 | 17.2 | 38.3 mg/d | 36.2% |
| Magnesium, mg/d | 290 | 294 | 314 mg/d | 47.5% |
| Potassium, mg/d | 2900 | 2778 | 2786 mg/d | n/a |

*69.8% pregnant women ages 20 to 40 years used dietary supplements

Bailey et al. *JAMA Network Open*. 2019;2(6):e195967.

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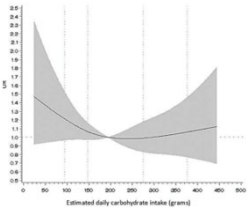
## Low CHO before pregnancy:
The National Birth Defects Prevention Study

- Restricted CHO diet 30% increased odds of neural tube defect
  - Adjusted for caloric intake, folic acid supplementation



Tail-restricted spline illustrating the relation between carbohydrate intake among women in the year before conception and risk of anencephaly or spina bifida in offspring, National Birth Defects Prevention Study, 1998–2011.

Desrosiers et al. *Birth Defects Res*. 2018.
Shaw GM, Yang W. *Birth Defects Res*. 2019.

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## Low CHO before pregnancy:
### Pre-folic acid fortification

- Examined low CHO intake and neural tube defects (1989-1991)
- n=449 mothers with spina bifida or anencephaly; n=458 controls
- *Restricted CHO* defined as ≤5th percentile among controls (~122 g/d)
- AOR 2.1 (1.3, 3.6) for *restricted CHO*
  - Adjusted for race/ethnicity, education, alcohol use, folic acid supplement
  - Adjustment for energy intake slightly attenuated AOR to 1.7 (1.0, 3.0)

"NTD risk with low CHO intake cannot be wholly function of low folic acid intake."

Shaw GM, Yang W. *Birth Defects Res*. 2019.

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## Low carb during pregnancy – infant outcomes

| Infant growth measure | Findings | CHO intake level | Confounders |
|---|---|---|---|
| Birth weight / size | • Decreased with CHO <45% in 1 study [2]<br>• BW increased with CHO increase (South Africa)[3]<br>• No difference in BW, LGA, or SGA[4] | (g CHO not reported)<br>56% vs 64%<br><br>32% vs 41% | Adjusted for energy<br><br>Energy intake<br>Energy intake |
| Birth length | • Increased with higher CHO[5] | IQR 182 – 272 g/d | Energy intake |
| Ponderal index / fat mass | • Increased with higher CHO[5]<br>• Lowest in lowest CHO quartile[6] | IQR 182 – 272 g/d<br>188 g/d vs 238 g/d | Energy intake<br>Adjusted for energy intake |
| Head circumference | • CHO ~100 g/d assoc with lower HC[7]<br>• Modestly low CHO assoc with smaller HC[8] | ~100 g/d threshold<br>135 g/d vs ~200 g/d | Energy intake |
| Gestational age at birth | • Older gestational age at birth with low CHO among overweight/obese mothers.[9] | 100 g/d vs 187 g/d | Energy intake |

1) Sweeting A, et al. *Nutrients*. 2021; 2) Morisaki et al. *Br J Nutr*. 2018; 3) Fahey CA, et al. *PLoS ONE*. 2019; 4) Harreiter J, et al. *Diabetes Care* 2019; 5) Eshak ES, et al. *Br J Nutr*. 2020; 6) Renault KM, et al. *Am J Clin Nutr* 2015;102:1475-81. 7) Powell CD, et al. PLoS ONE. 2020; 8) Mijatovic J, et al. *Am J Clin Nutr*. 2020; 9)Tanner H, et al. *Nutrients*. 2021;13(10).

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## Low CHO during pregnancy

- Examine low CHO diet among overweight/obese pregnant women
- N=411
- Diet data at 16 wk and 28 wk gestation
- Compared lowest CHO intake quintile to Q2-5

| | Q1 (n=42) | Q2-5 (n=266) | *p* |
|---|---|---|---|
| **CHO, g** | 100 (16) | 187 (48) | <0.05 |
| **Folate, mcg** | 150 (36) | 258 (76) | <0.05 |
| **Thiamin, mg** | 0.8 (0.2) | 1.5 (0.5) | <0.05 |
| **Gestational age, wk** | 39.8 (1.2) | 39.1 (1.9) | <0.05 |
| **Birth centile** | 43 (29) | 53 (30) | 0.005 |

Tanner H, et al. *Nutrients*. 2021;13(10)

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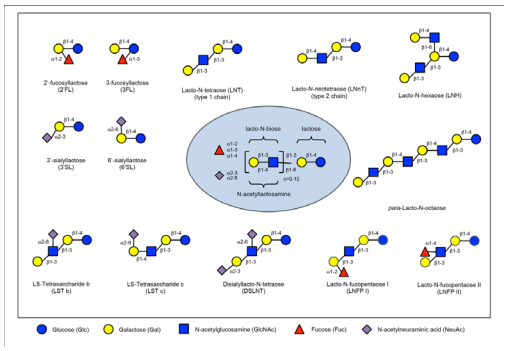


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