Implications of Maternal Weight and Metabolic Status for Lactation and Breastmilk Composition

National Academy of Sciences Workshop

"Nutrition During Pregnancy and Lactation-Exploring New Evidence"

January 29-30, 2020

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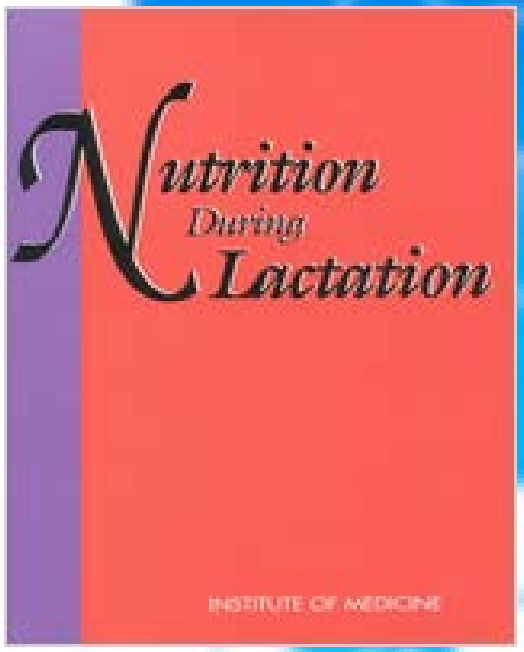
Topics covered in this presentation

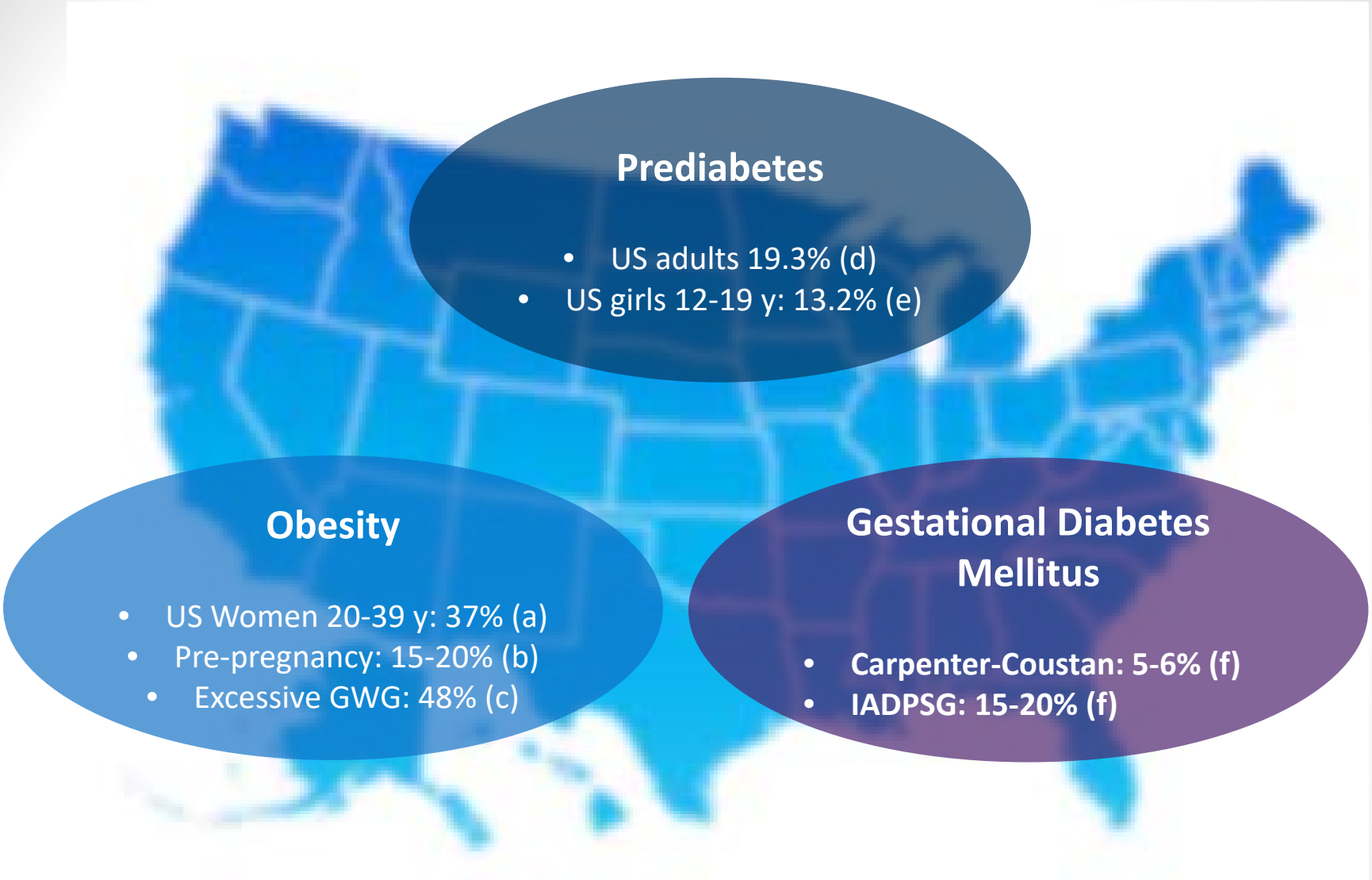
- Maternal obesity and diabetes in the US; lactation as a sensitive period for maternal and infant programming
- Evidence linking maternal obesity and metabolic health to *lactation and breastfeeding indicators*
- Evidence linking maternal obesity and metabolic health to *human milk composition variation*
- Summary and Implications



1990 Prevalence

- Adult Obesity: 11.4%
- Gestational Diabetes: 2%

Nutrition During Lactation. Institute of Medicine (US) Committee on Nutritional Status During Pregnancy and Lactation. Washington (DC): National Academies Press. 1991.



Prediabetes

- US adults 19.3% (d)
- US girls 12-19 y: 13.2% (e)

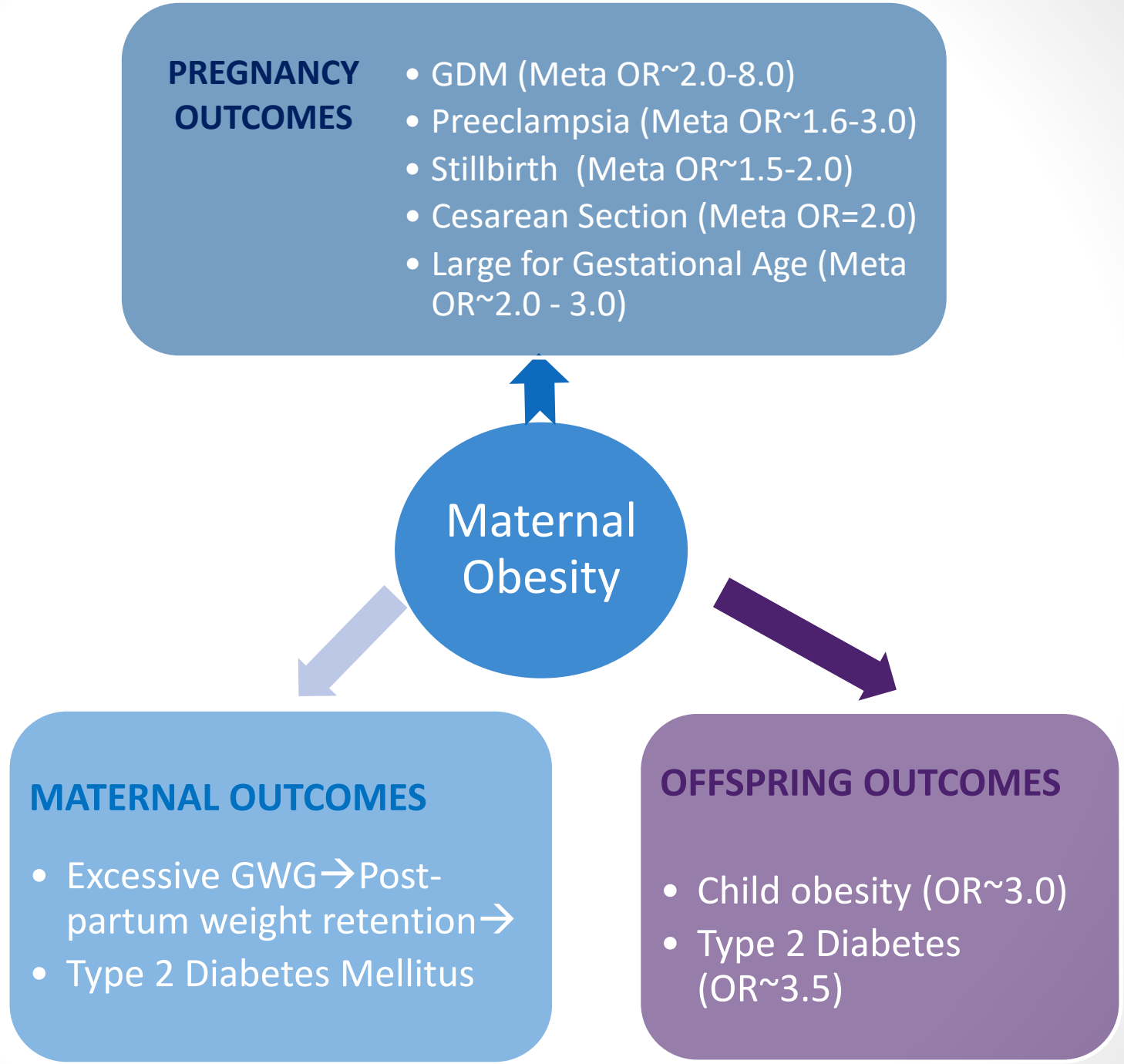
Obesity

- US Women 20-39 y: 37% (a)
- Pre-pregnancy: 15-20% (b)
- Excessive GWG: 48% (c)

Gestational Diabetes Mellitus

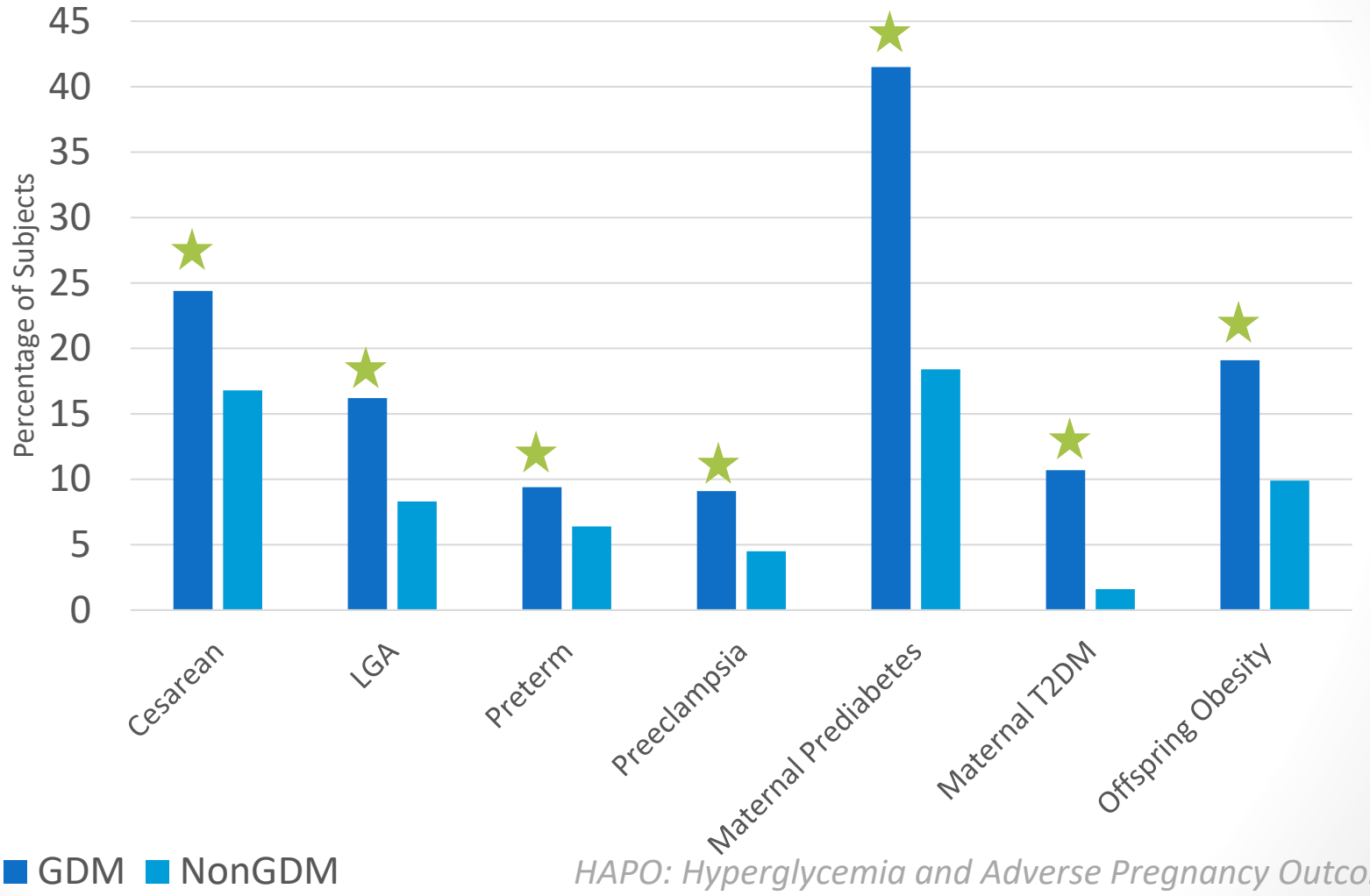
- **Carpenter-Coustan: 5-6% (f)**
- **IADPSG: 15-20% (f)**

a: Flegal et al. 2016 JAMA. 315:2284
b: Branum et al. 2016 National Vital Stat. Reports 65 (6).
c: MMWR Morb Mortal Wkly Rep 2016;65:1121
d: Menke et al. Ann. Epidemiol 218. 28:681.
e: Menke et al. 2018. JAMA. 316:344.
f: NIH Consensus Panel 2013. Obstet Gynecol. 122: 358.



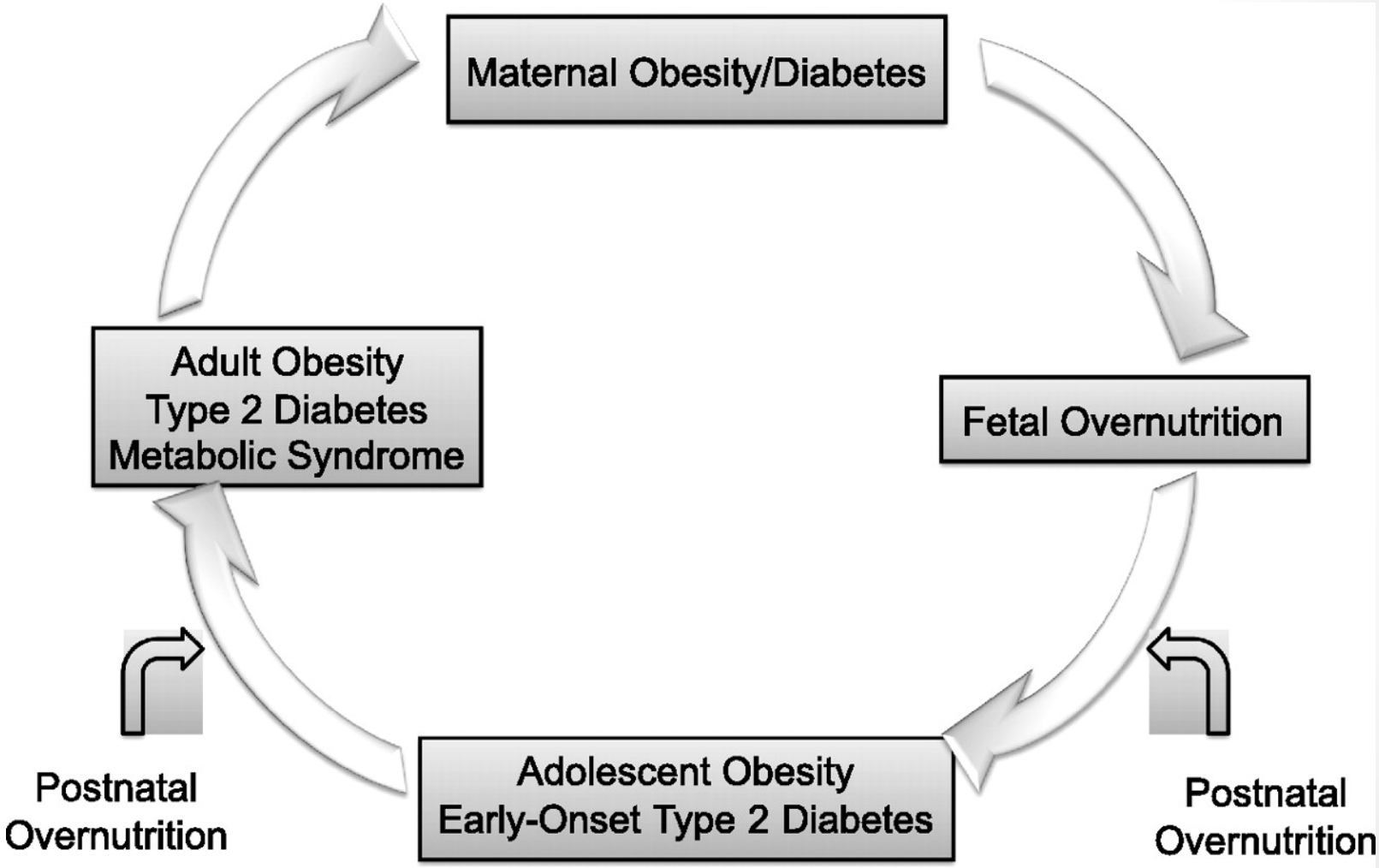
Reviewed by Catalano and Shankar BMJ 2017; 356:j1.; Kulie et al. J Am Board Fam Med 2011;24:75– 85; Lahti-Pulkkinen et al. *Diabetologia* **62,** 1412–1419 (2019)

Perinatal and long-term outcomes in women classified with GDM or non GDM; HAPO and HAPO Follow-Up

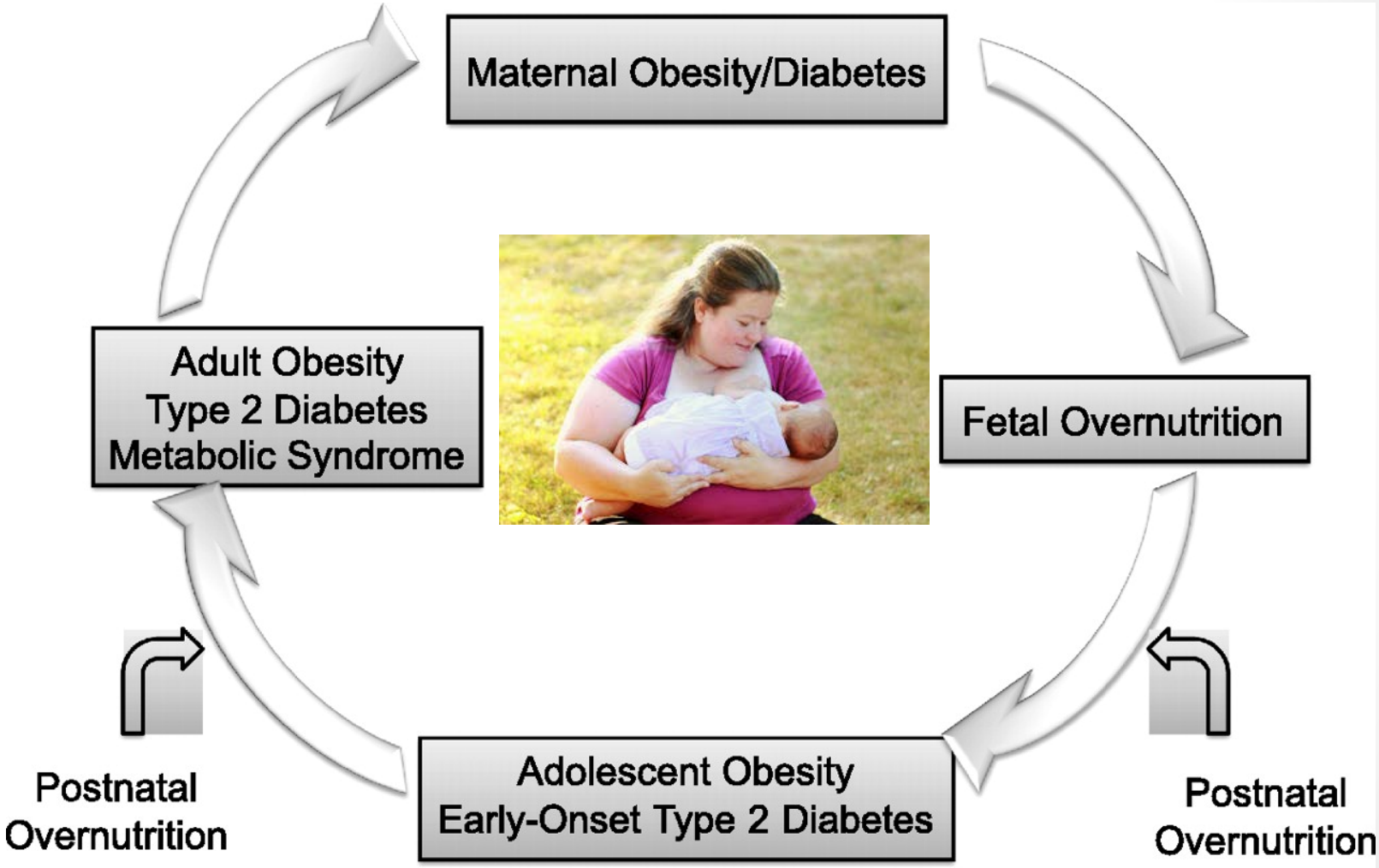


HAPO: Hyperglycemia and Adverse Pregnancy Outcome
Data from Hod et al. 2019 Am. J. Obstet Gynecol. 221:109.
★ *p<0.001*

Intergenerational and Developmental Origins of Obesity and Diabetes

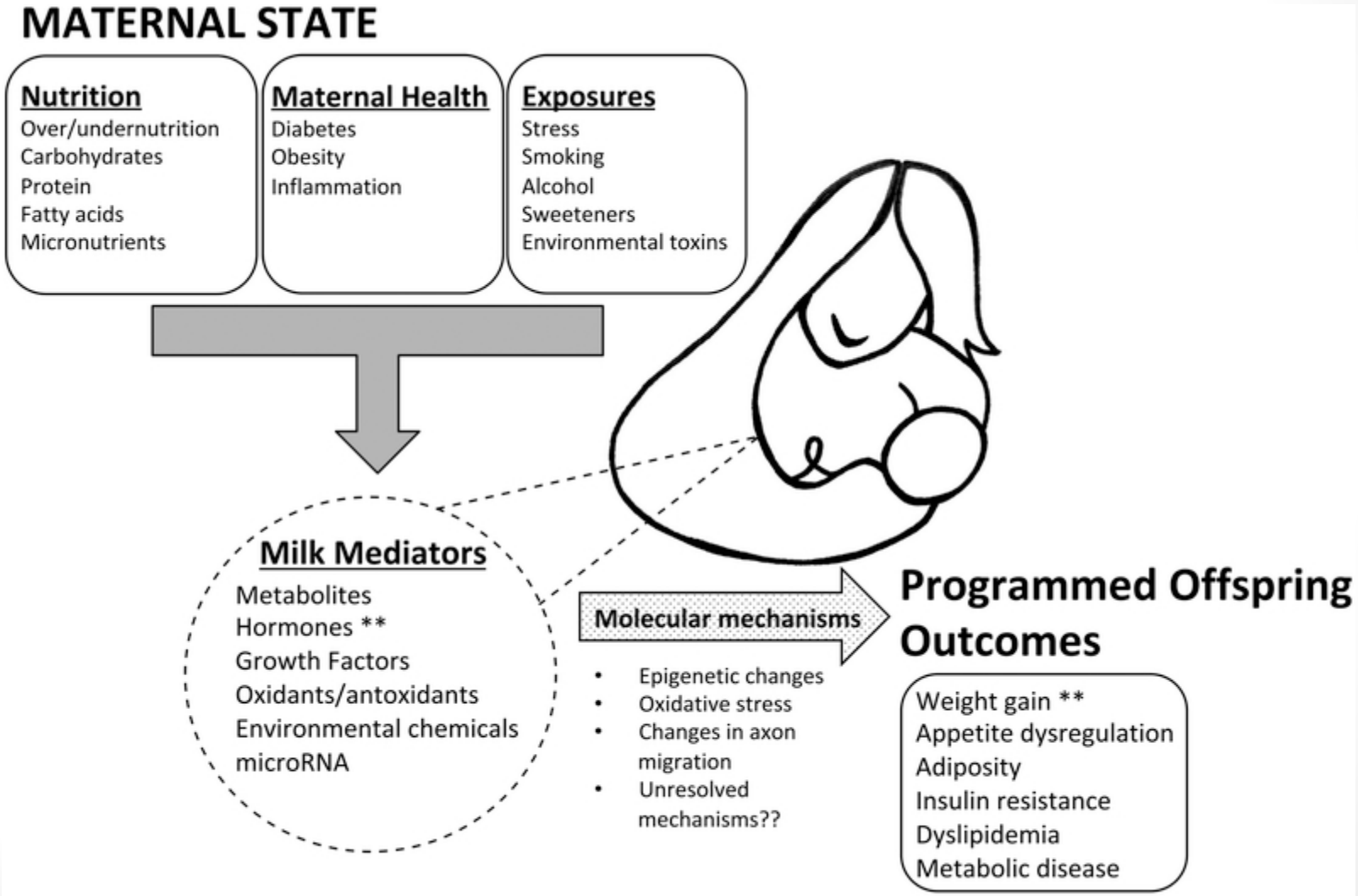


From; Dabelea and Crume Diabetes 2011 Jul; 60(7): 1849-1855.



From; Dabelea and Crume Diabetes 2011 Jul; 60(7): 1849-1855.

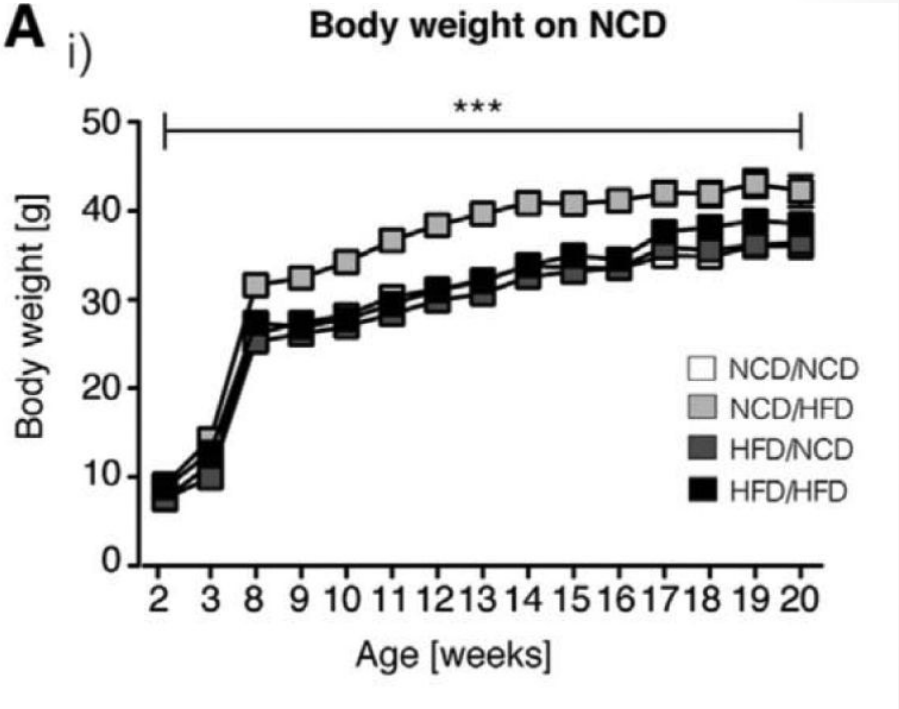
Concept of Lactational Programming



From: Ellsworth et al. Reproduction. 2018 Aug;156(2):R23-R42.

Proof of concept: Rodent models show lactation as a critical period for programming of appetite

- Maternal high fat diet *exclusively during lactation* (NCD/HFD group)
  - Increased milk glucose and insuli
  - Reduces density of neuronal fibe in hypothalamic melanocortin an AgRP projections involved in appetite regulation
  - Had life-long effect on offspring metabolic function
  - Increased offspring body weight, adiposity, glucose tolerance, despite low fat diet post-weaning



Vogt et al. *Cell*. 2014 ; 156(3): 495–509

Nonetheless……benefits of greater breast feeding for mother and infant

- Documented benefits for mothers:
  - Breast and ovarian cancers, post-partum weight retention, T2DM
- Documented benefits for infants and children:
  - Gastrointestinal, respiratory disease
  - Cognition
  - Childhood obesity

- Breastfeeding modifies metabolic risk transmission
  - SWIFT study: Intensive breastfeeding in infants of GDM mothers was associated with lower infant weight status in first year (Gunderson et al. 2018 *Ped. Obes*.)
  - Breastfeeding ≥6 months mitigated the effects of GDM exposure on childhood adiposity at 6-13 y (Crume et al. Diabetes Care 2011. 34(3):641.)
  - GUTS Study: Exclusive breastfeeding associated with lower risk of childhood obesity (OR=0.66 (0.53-0.82); did not vary by maternal obesity or diabetes status (Mayer-Davis et al., Diabetes Care. 2006;29(10):2231)
  - Compared to NW women, increased risk of childhood obesity among obese women was lower in those breastfed >4 mos (OR = 3.5) vs. never breastfed (OR = 6.1) (Li et al., Obes Res. 2005;13:362)

Two truths and a couple of ~~lies~~...

erroneous assumptions

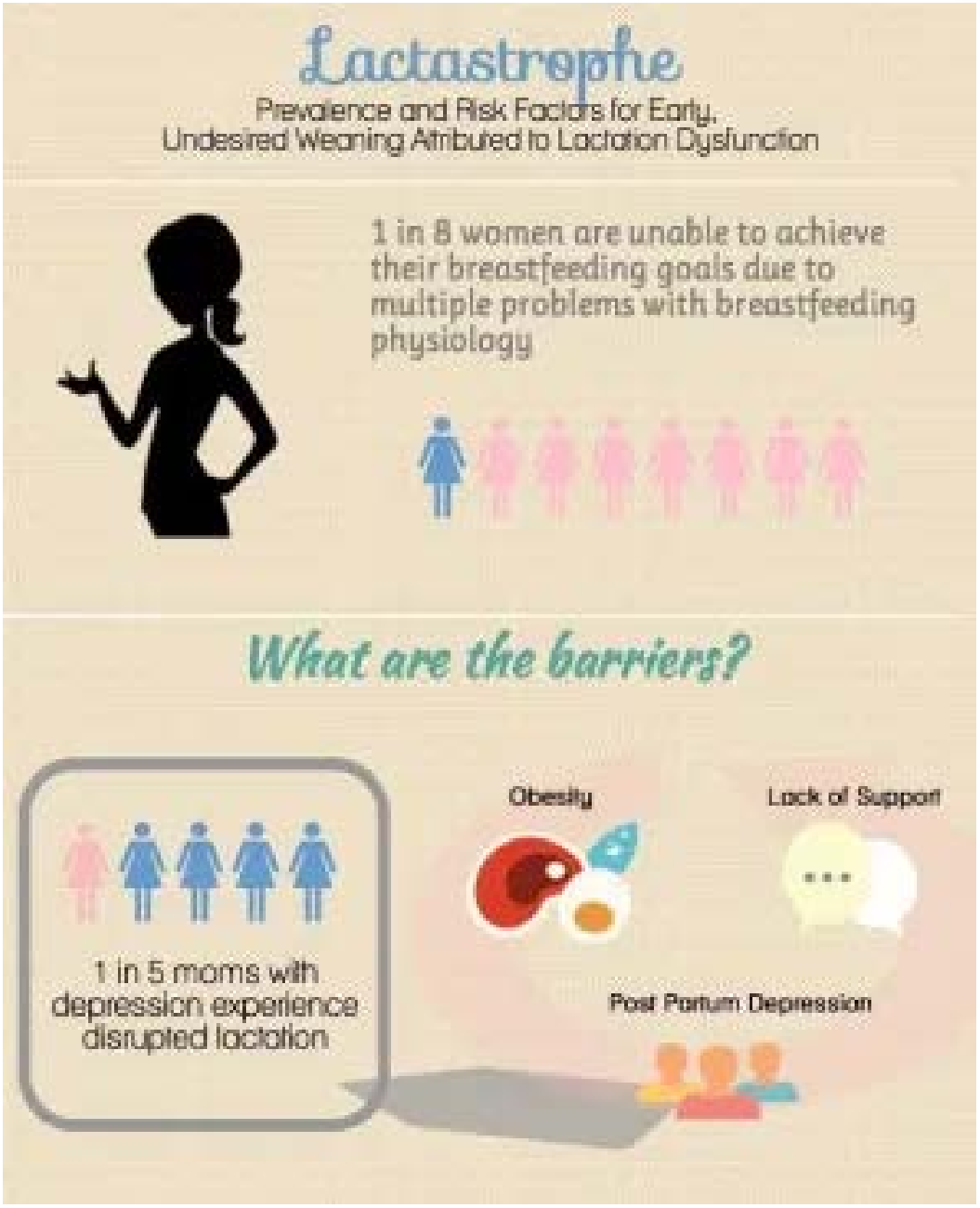
- Truth→ Breastfeeding has important health benefits for mothers and their infants as compared to formula feeding, including for women with obesity and diabetes

- Truth→ Breastfeeding has numerous health benefits for mothers and their infants, including for women with obesity and diabetes
- Erroneous assumption→ Any observed maternal metabolic status relationships with breastfeeding outcomes are entirely social, not biological.

- Truth→ Human milk contains hundreds of nutritional and non-nutritional factors that make it superior to formula for infant development

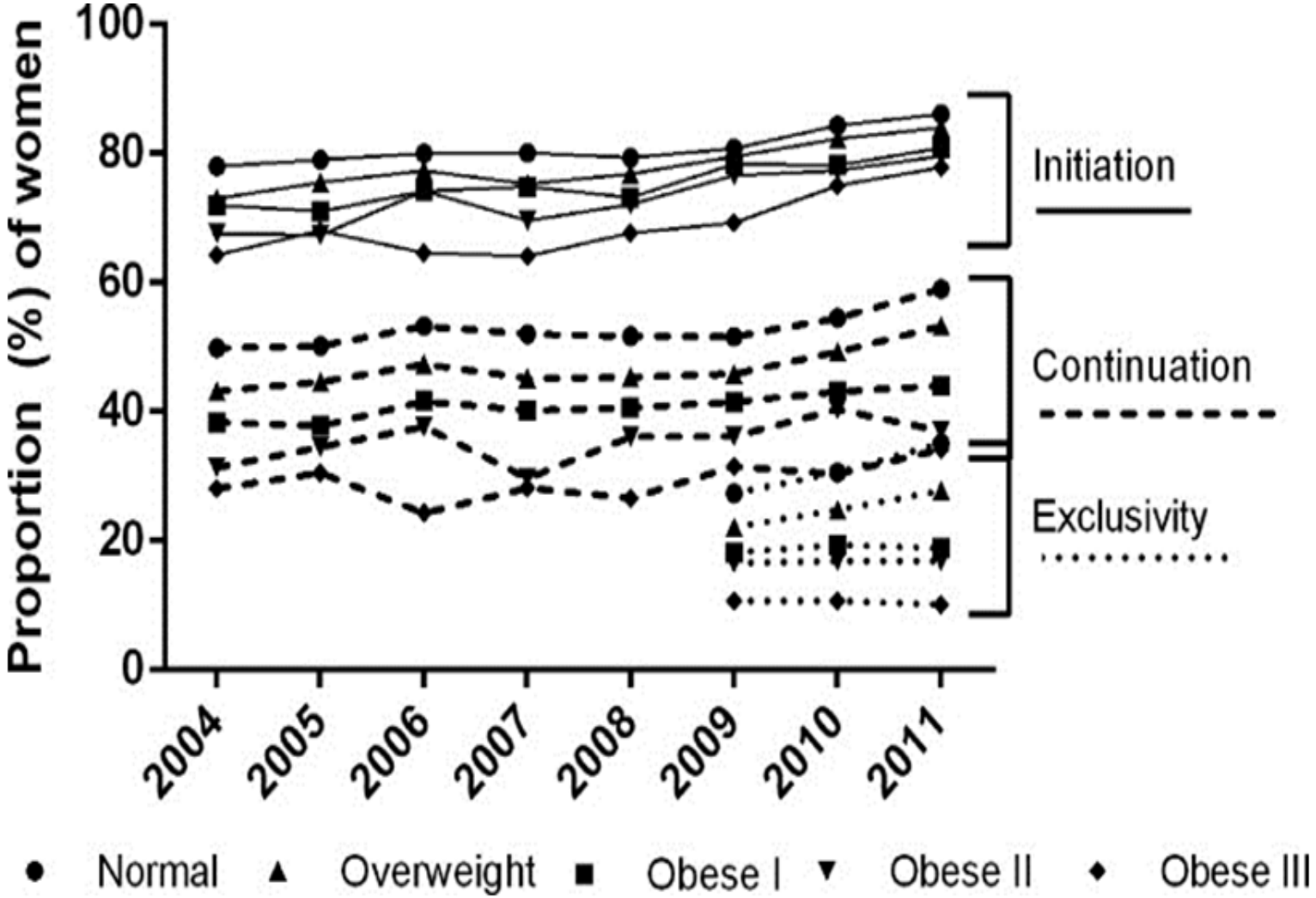
- Truth→ Human milk contains hundreds of nutritional and non-nutritional factors that make it superior to formula for infant development
- Erroneous assumption→ Human milk composition is essentially uniform across women; maternal obesity and diabetes do not alter it.

Evidence linking maternal metabolic status and breastfeeding outcomes



From: Steube et al. *J Womens Health (Larchmt).* 2014 May;23(5):404-12.

Trends in breastfeeding outcomes by maternal pre-pregnancy weight; PRAMS 2004–2011



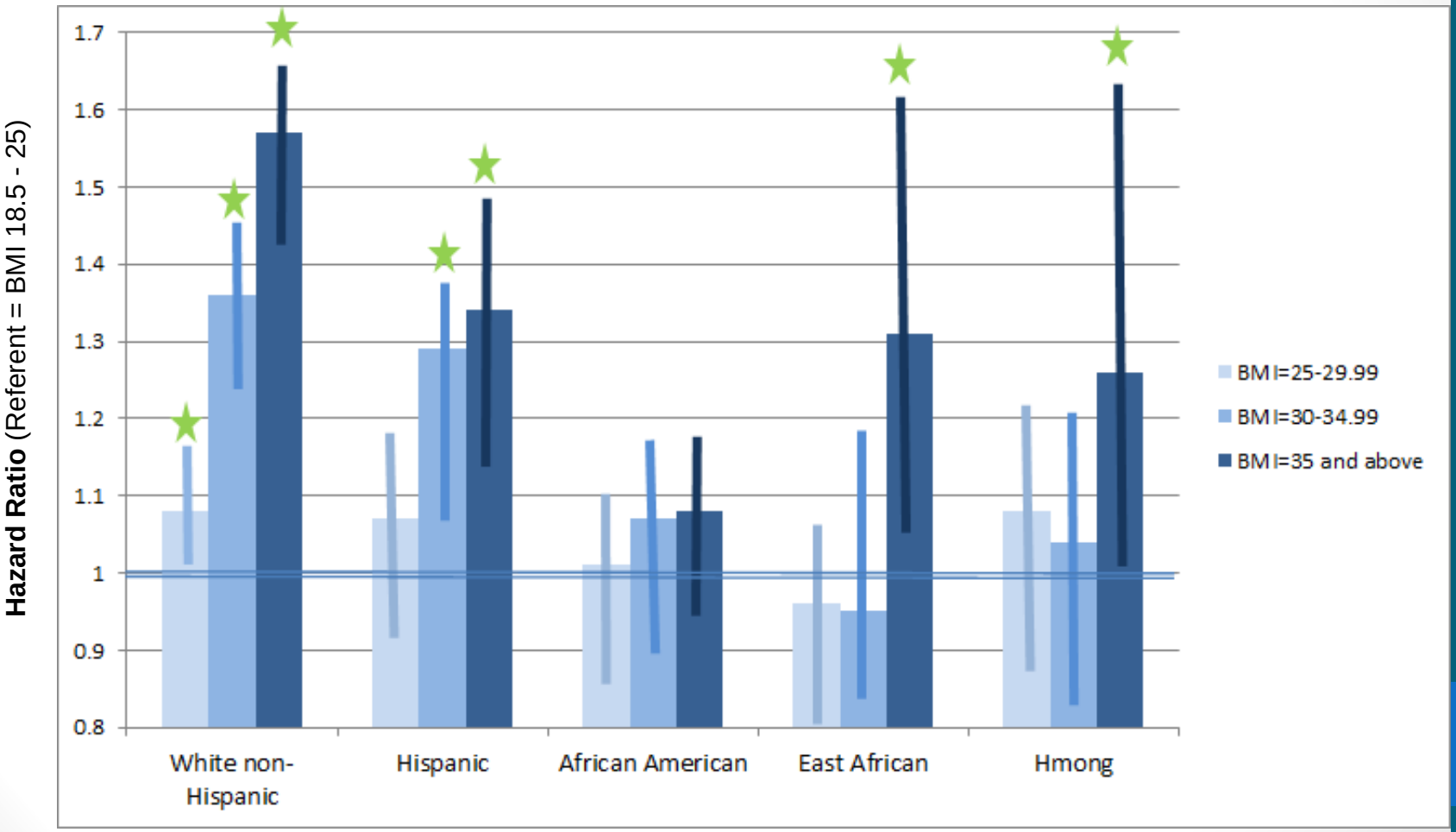
Obesity, Volume: 23, Issue: 9, Pages: 1895-1902, First published: 03 August 2015, DOI: (10.1002/oby.21151)

Maternal obesity and lactation

- Delayed prolactin release (> 2 days)
- Lower prolactin response to suckling
- Lower milk transfer at 60 hours post delivery
- Higher rate of cesarean section/prolonged labor
  - **Delayed lactogenesis II**
  - **~15% lower rate of breastfeeding initiation**
- More difficulty in positioning and latch
- Less body confidence and comfort in public
- Likely others… (lower employer accommodations, etc)
  - **Shorter breastfeeding duration**

Rasmussen (2001) J Nutr, 131(11), 3009s–11s.; Baker et al (2007) Am J Clin Nutr, 86(2), 404–411; Kachoria et al. (2015) Obesity, 23(9), 1895–1902.; Kitsantas et al (2011). J Perinat Med, 40(1), 77–83; Li et al (2003) Am J Clin Nutr, 77(4), 931–936. Nohr et al (2009) PLoS One, 4(12), e8444; Scott-Pillai et al (2013). BJOG 120(8), 932–939. Thompson et al. (2013) Matern Child Health J, 17(10), 1842–1851; Mok et al., (2008) Pediatrics 121: E1319-1324.

Maternal pre-pregnancy BMI status and risk of any breastfeeding cessation by 6 months post-partum among 81,669 Minnesota WIC participants, 2012-2016



In preparation: Marino et al. Association between maternal pre-pregnancy body mass index (BMI) and breastfeeding cessation by race among 81,669 breastfeeding women enrolled in Minnesota WIC. Unpublished Masters' Thesis, University of Minnesota School of Public Health, 2018

Associations with Gestational Diabetes

- SWIFT Study: 1/3 of C-C dx-GDM women experienced delayed onset of lactation; insulin tx, maternal obesity risk (Gunderson et al., 2017; Am J Clin Nutr doi: 10.3945)
- Women with GDM were less likely to breastfeed(OR = 0.77; CI:= 0.68–0.87) compared to non-GDM women (Finkelstein et al. *Diabet Med.* 2013; 30(9):1094-101)
- No influence of self-reported GDM diagnosis on breastfeeding duration in ~4,000 women in the IFPS Study II (Wallenborn et al. *J Pregnancy*. 2017;2017:9581796)

Leptin, insulin, and cortisol as possible mechanisms

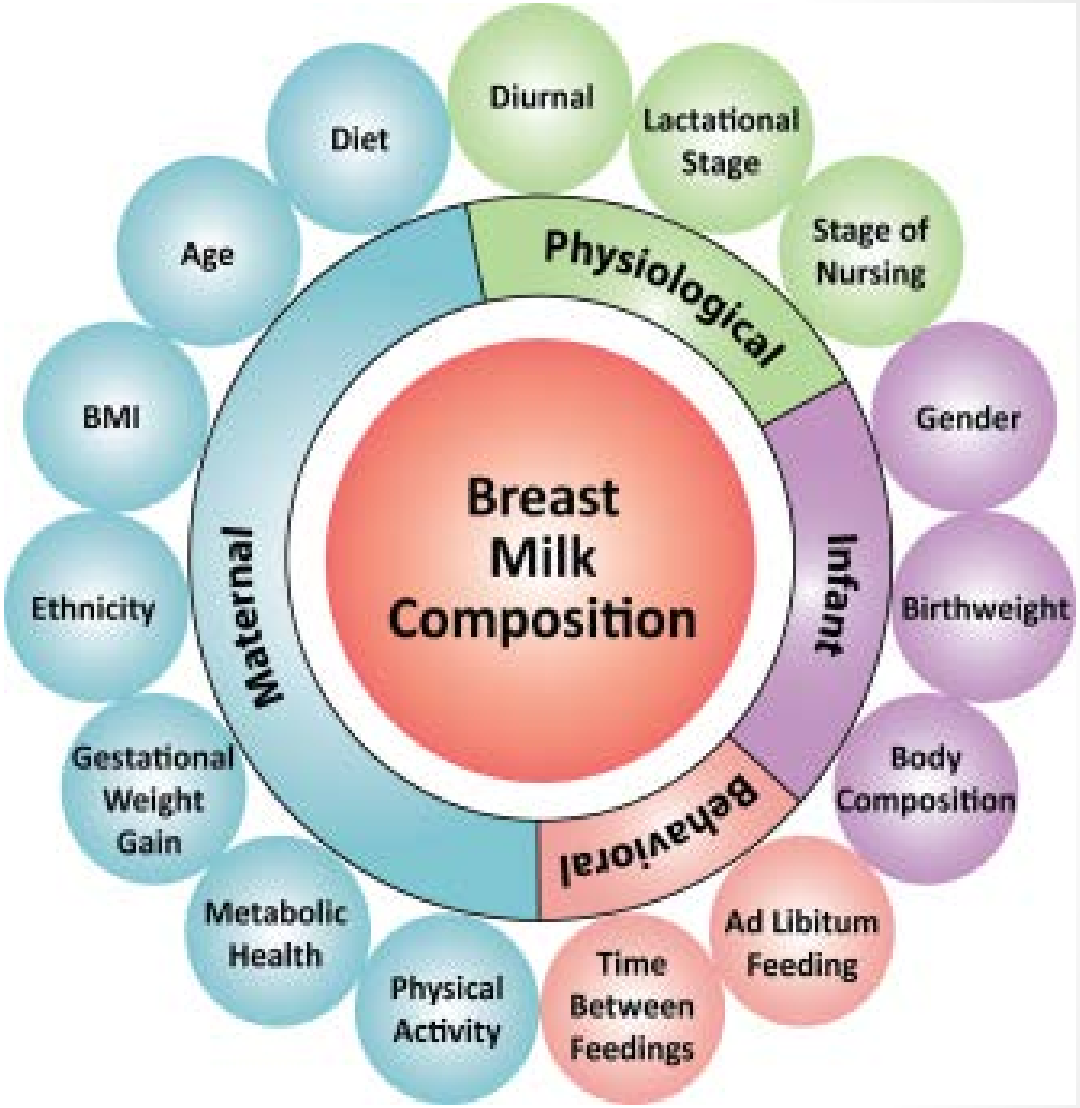
- Leptin
  - Inhibits oxytocin's effect on muscle contractions *in vivo*, possibly depressing milk ejection reflex (*Moynihan et al. Am J Obstet Gynecol. 2006 Aug; 195(2):504-9)*
  - May cause prolactin resistance, inhibiting the positive effects of prolactin on milk production [Buonfiglio et al., 2016 . *Sci Rep*, *6*, 22421.)
- Insulin
  - Stimulates the expression of genes directly involved in milk protein synthesis; IR reduces protein tyrosine phosphatase, receptor type F (PTPRF) expression, necessary for milk production (Lemay et al., PLoS One 2013;8:e67531.)
  - Insulin signaling is critical to normal mammary differentiation and to milk secretion at the level of the lactocyte (Neville et al. Am J Physiol Endocrinol Metab. 2013 Nov 1; 305(9):E1103-14.)
- Cortisol
  - May suppress insulin action, prolactin

Implications…

- Trials testing intensive breastfeeding support before and immediately after birth targeting obese and diabetic women are needed to advance our understanding of the causal relationships and to improve breastfeeding rates
- Bi-directional relationship of lactation and maternal obesity and diabetes must be considered in observational studies of the maternal health benefits of lactation, as they are confounded to some extent by metabolic status prior to or during pregnancy.

Evidence linking maternal metabolic status and breast milk composition

- ***Over 1000 compounds***
  - *Gross Composition*
  - *Fatty acids*
  - *Hormones*
  - *Immune Factors, Antimicrobials*
  - *Oligosaccharides*
  - *Microbiomes*
  - *Environmental pollutants*
- Multiply determined by physiological, behavioral, environmental, maternal and infant factors



From Fields et al. (2016) Obesity. 24 (6): 1213–1221

Some general observations on milk composition

- Milk composition often mirrors maternal serum composition
- Maternal [serum]/[milk] are positively correlated with one another for most bioactives studied to date
- Milk concentrations may be higher or lower than in maternal serum
  - Adiponectin higher
  - Fatty acids, leptin, insulin lower

- Milk concentrations typically decline over lactation:
  - From colostrum to mature milk
  - From early to later mature milk

- Gap: milk composition after 6 months has been little studied
- Limitation: Mostly observational and generally small (N<150 women) studies

a. Whitaker et al. Obesity 2017; Savino et al., Nutrients. 2016 Jun 21;8(6).

Maternal metabolic status and milk *macronutrient* composition

- DARLING study found increased milk lipid in mothers with higher relative weight (Nommesen et al. *Am J Clin Nutri.* 1991; 53(2):457-465)
- Other studies have found either very small or no significant differences in total milk lipid, protein or lactose concentrations across maternal pre-pregnancy BMI or gestational weight gain groups (Michaelsen et al. Am J Clin Nutr. 1994; 59: 600-611; Quinn et al. Am J Hum Biol. 2012; 24: 533-540; Chang et al. *Nutr Res Pract*. 2015; 9(4):433-438.)

Maternal metabolic status and milk *fatty acid* and *micronutrient* composition

- Recent review from scientists at the USDA Nutrient Data Laboratory notes that US nutrient reference data for human milk is out of date, based on small numbers of mostly normal weight women and using older methods (Wu et al., 2018. *Curr Dev Nutr* 2018;2:nzy025)
- Lower milk omega-6 LCPUFA (EPA and DHA) and higher omega-3 LCPUFAs in obese vs lean women (Panagos et al., J. Perinatol. 2016 Apr;36(4):284-90; Garcia-Ravelo et al., 2018)
- Milk from obese mothers also had decreased levels of carotenoids and Vitamin D (Panagos et al., 2016).
- Evidence of maternal metabolic conditions (obesity, glucose dysregulation) on micronutrients is lacking for most other:
  - Vitamins
  - Minerals
  - Polyphenols

Human Milk Nutrient Composition in the United States: Current Knowledge, Challenges, and Research Needs

Xianli Wu,[1] Robert T Jackson,[2] Saira A Khan,[2] Jaspreet Ahuja,[1] and Pamela R Pehrsson[1]

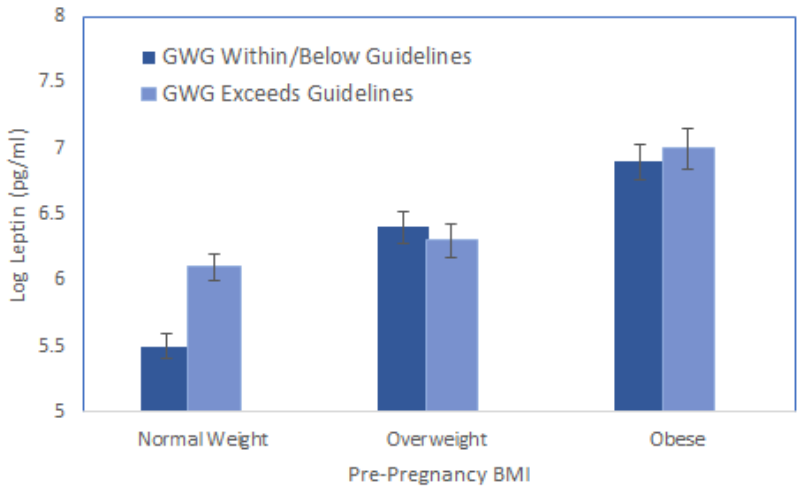
[1]Nutrient Data Laboratory, USDA ARS Beltsville Human Nutrition Research Center, Beltsville, MD and
[2]Department of Nutrition and Food Science, University of Maryland, College Park, MD

Milk bioactive elements most frequently studied in relationship to maternal metabolic status

- Hormones altered in serum of obese adults that regulate *appetite, satiety, and metabolism:*
  - Leptin
  - Insulin
  - Ghrelin
- Hormones and cytokines altered in obesity and involved in *immune response/ inflammation*
  - Adiponectin
  - Cytokines/acute phase reactants
- We are just scratching the surface

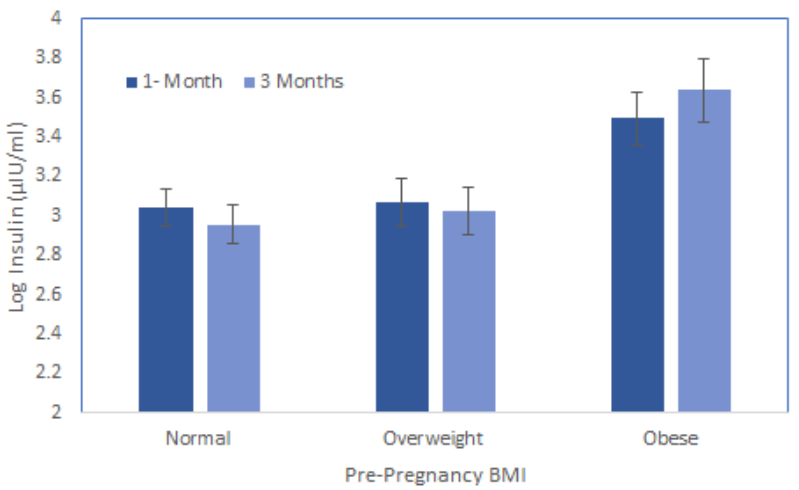
- Most consistent finding in the literature: Positive association of maternal pre-pregnancy BMI with milk leptin and insulin

Milk Leptin by GWG Category and Maternal Pre-Pregnancy BMI



BMI: p < 0.0001
GWG: p = 0.007
BMI*GWG: p=0.02

Milk Insulin at 1- and 3 Months by Maternal Pre-Pregnancy BMI Category

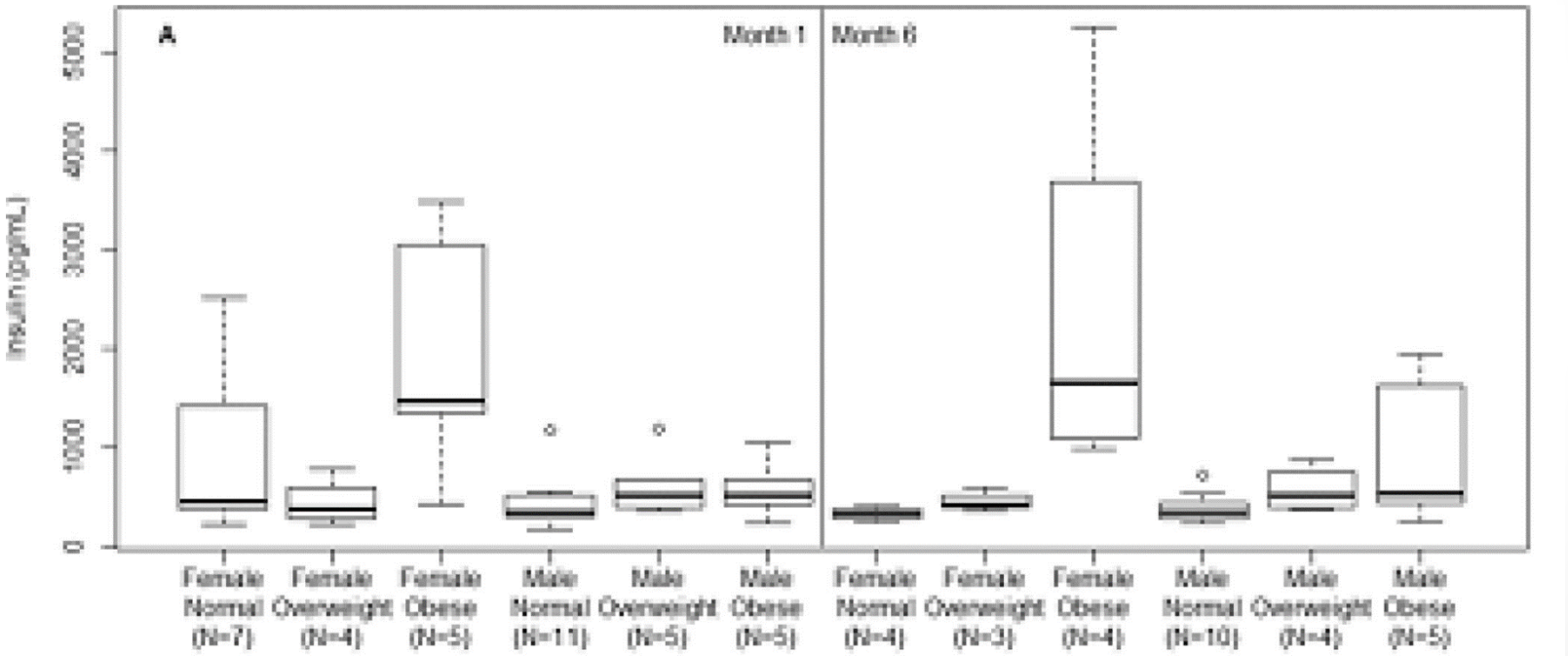


BMI: p = 0.03
Time: p = 0.94
BMI*Time: p = 0.02

From Whitaker et al., 2017 Obesity 26(10):1659-1660; sadr Dadres et al. 2019 *Obesity* 27(4):621-628 Fields & Demerath 2012, Young et al. 2017.

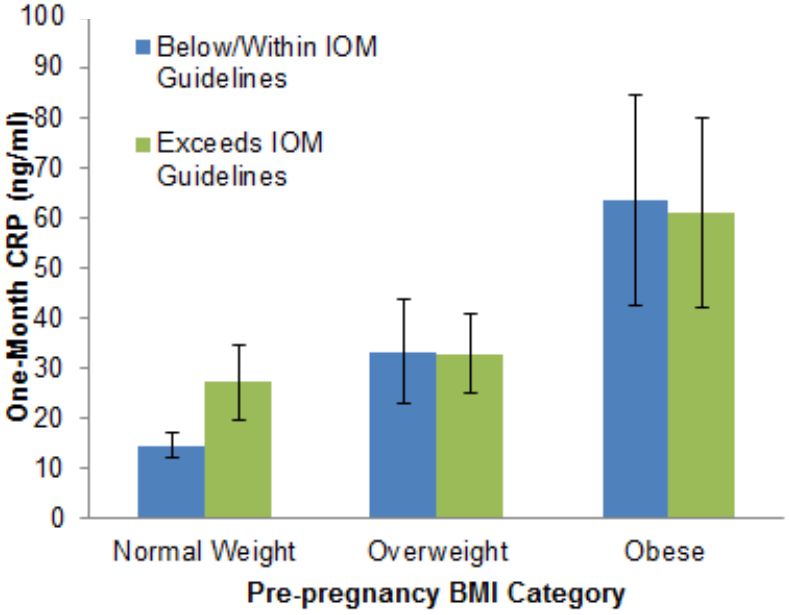
Maternal BMI-milk insulin relationship stronger in milk for female infants

p for interaction (infant sex x BMI) = 0.03



Fields et al. Pediatr Obes. 2017 Aug;12 Suppl 1:78-85.

Milk CRP



Whitaker et al. Obesity. (2017)

Milk IL-6

- **Greater** milk IL-6 in obese vs normal weight women (Collado et al *Pediatr. Res*., 2012)
- **No association** of maternal BMI or GWG with milk IL-6 concentration at 1 and 3 months (Whitaker et al. *Obesity* 2017)

Milk Adiponectin

- Martin et al. *AJCN*, 2006: Concurrent BMI **positively** associated with milk adiponectin (N=22 with serial data)
- Ley et al. *AJCN*. 2012: **no association** of pre-pregnancy BMI or insulin sensitivity with milk adiponectin in colostrum or 3 mo milk. (N=170)
- Chan et al., *IJO*. 2018: **No association** of pre-pregnancy BMI with milk adiponectin at 4 months (N=430)
- Sadr Dadres et al *Obesity* 2019: Pre-pregnancy BMI **negatively associated** with adiponectin; stronger association at 1 month than 3 mos.(N=135 with serial data)

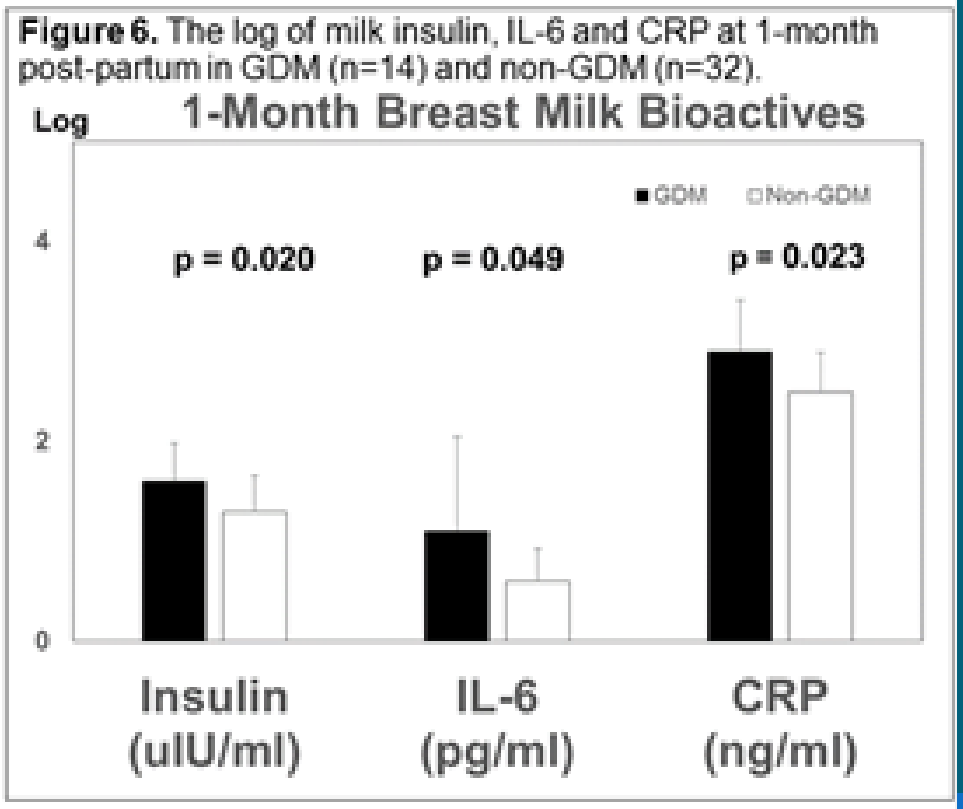
Maternal obesity and altered milk immunological function

Reviewed by Erliana and Fly (2019) *Nutrients* 2019, 11, 1284, covered publications from 1980-2017:

- Antimicrobials→ one study
- Cells (e.g., macrophages)→2 studies
- Cytokines (e.g., IL-6, TNF-alpha)→ 3 studies;
- Chemokines→ no studies
- Intestinal growth factors→ no studies
- Immunoglobulins→6 studies; inconsistent results

Evidence on relationship of maternal diabetes to milk composition

- Breastmilk insulin and glucose are elevated in women with Type I and Type II diabetes (a,b,c,)
- Ghrelin is lower in colostrum of women with GDM and pre-existing diabetes compared to nondiabetic women, but no difference in mature milk at day 15 (d)



a) Schaefer-Graf et al. Diabetes Care 2006. 29:1105–1107; b) Whitmore et al. International Journal of Endocrinology. 2012;2012:296368. c) Jovanovic-Peterson et al. J Am Col Nutr. 1989;8(2):125-31. d) Aydin et al. Nutrition. 2007;23(11-12):807-11; e) *Unpublished data from MILk (Fields and Demerath, 2019)*

Milk metabolomic differences by maternal BMI

- 275 metabolites were quantified in human milk by LC-MS in a subset of 35 MILk Study subjects
- At 1-month, 9 metabolites were different in the overweight/obese vs and normal BMI group (3/9 were milk oligosaccharides) ($q<0.05$)
- Milk adenine and 5-methylthioadenosine were positively associated with both maternal BMI and infant weight and body fatness ($q<0.05$ for both)

Isganaitis et al (2019). Am J. Clin. Nutr. 110 (1): 111–120

Maternal metabolism, HMOs, and the milk microbiome

- A significantly different and less diverse microbiome in human milk with higher maternal BMI *(Cabrera-Rubio et al Am J Clin Nutr. 2012 Sep; 96(3):544-51.)*
- *Bifidobacterium* (lower) and *Staphylococcus (*higher) in obese as compared to normal weight women *(Delzenne & Cani, 2011; Collado et al., 2012)*
- No association of pre-pregnancy BMI with HMO concentration in the CHILD study *(Azad et al., J. Nutr. 2018, 148, 1733–1742)*

Evidence for milk components influencing infant growth in humans is sparse but growing

REPRODUCTION

REVIEW

Lactational programming of glucose homeostasis: a window of opportunity

Lindsay Ellsworth, Emma Harman, Vasantha Padmanabhan and Brigid Gregg

Depa

Corres

REVIEW

CURRENT OPINION

Human milk composition and infant growth

Kamilla G. Eriksen, Sophie H. Christensen, Mads V. Lind, and Kim F. Michaelsen

nutrients

MDPI

Communication

Hormones in Breast Milk and Effect on Infants' Growth: A Systematic Review

Alessandra Mazzocchi [1], Maria Lorella Giannì [1,2], Daniela Morniroli [1,2], Ludovica Leone [1], Paola Roggero [1,2], Carlo Agostoni [1,3,*], Valentina De Cosmi [3] and Fabio Mosca [1,2]

Implications

- Up to 50% of US women do not reach their breastfeeding goals; additional lactation support is needed for obese and diabetic women who are at higher risk

- Research gaps regarding maternal nutrition and milk composition are many:
  - Updated information on human milk micronutrient and nonnutritive composition is needed for US women today
  - The research base on non-nutritive bioactives is growing but due to cost of laboratory analyses, sample sizes are often small for examining complex interactions among maternal and other determinants of milk composition
  - Studies are often hard to compare due to differences in design (stage and exclusivity of lactation, among others)
  - Most studies remain too small for adequate confounder adjustment, methodological variation, include mostly high SES white women, and look at only a handful of milk components in isolation

- Donor milk banks standardize milk for macronutrients but not hormones, oligosaccharides, etc.; further research on effects of pasteurization and donor characteristics in milk banks and online milk sharing is warranted

National Academy of Sciences Workshop

“Nutrition During Pregnancy and Lactation-Exploring New Evidence”

January 29-30, 2020