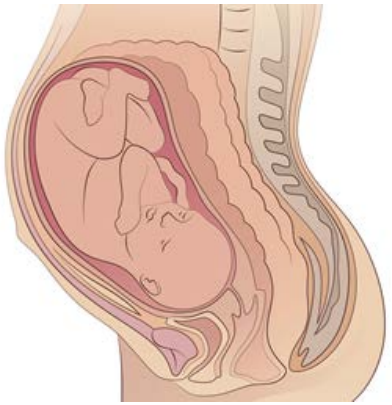


Choline: Exploring The Growing Science On Its Benefits For Both Mothers and Infants

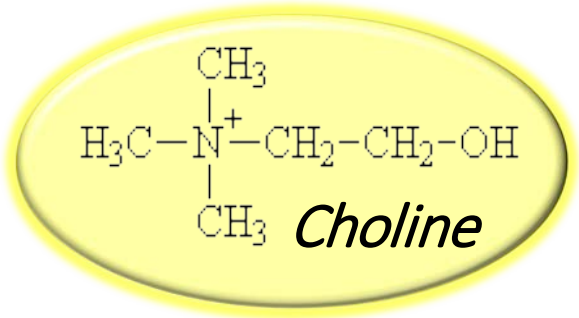
Marie A. Caudill, PhD, RD

Division of Nutritional Sciences

Cornell University, Ithaca, NY

Choline Plays A Critical Role In Fetal Development

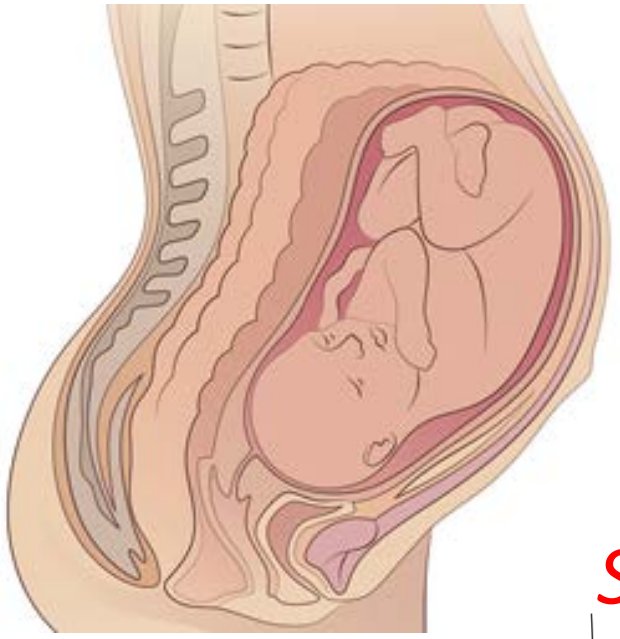
Choline Is Required For Fetal Growth

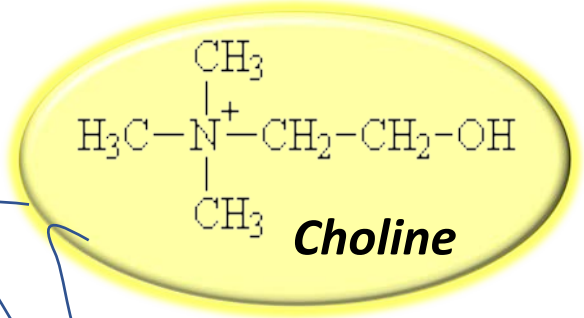


Phosphatidylcholine

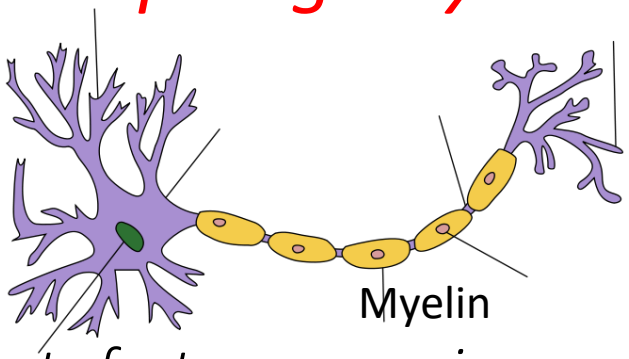
- Main constituent of cell membranes
- Large amounts are required for cell division and tissue expansion
- Required for export of lipid from maternal liver by VLDLs

Choline Is Required For Development Of The Central Nervous System





Sphingomyelin

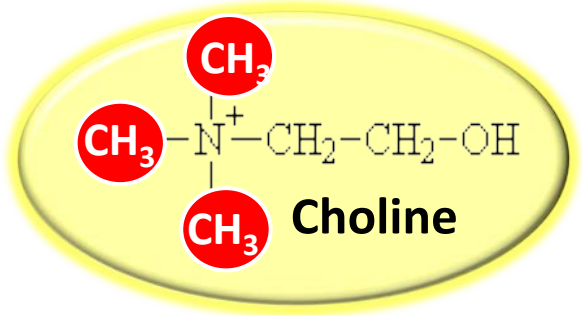


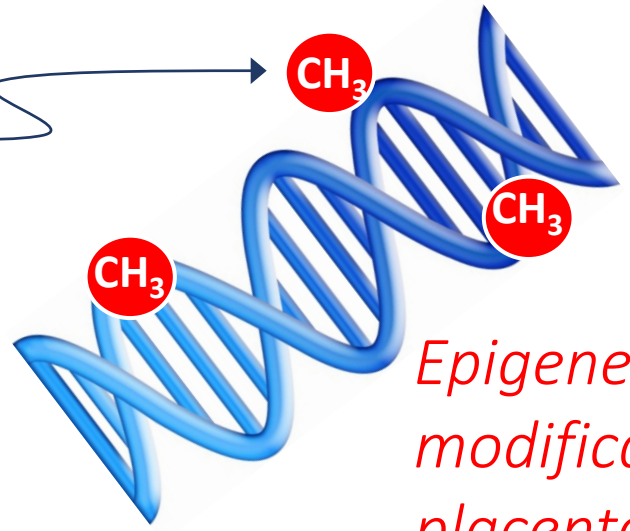
Supports faster processing speed

Acetylcholine

- Learning
- Memory
- Attention

Choline Is Required For DNA Methylation

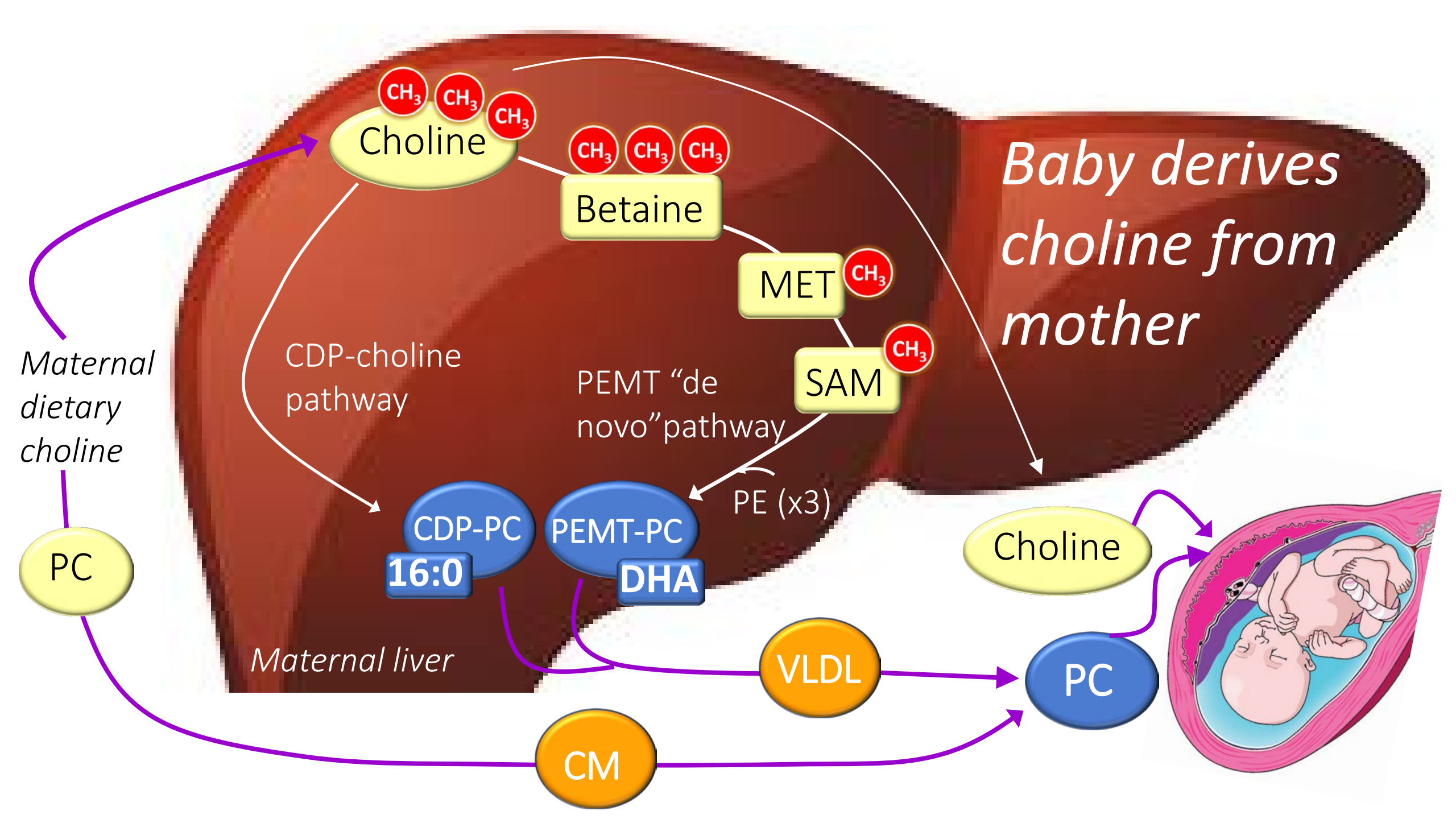




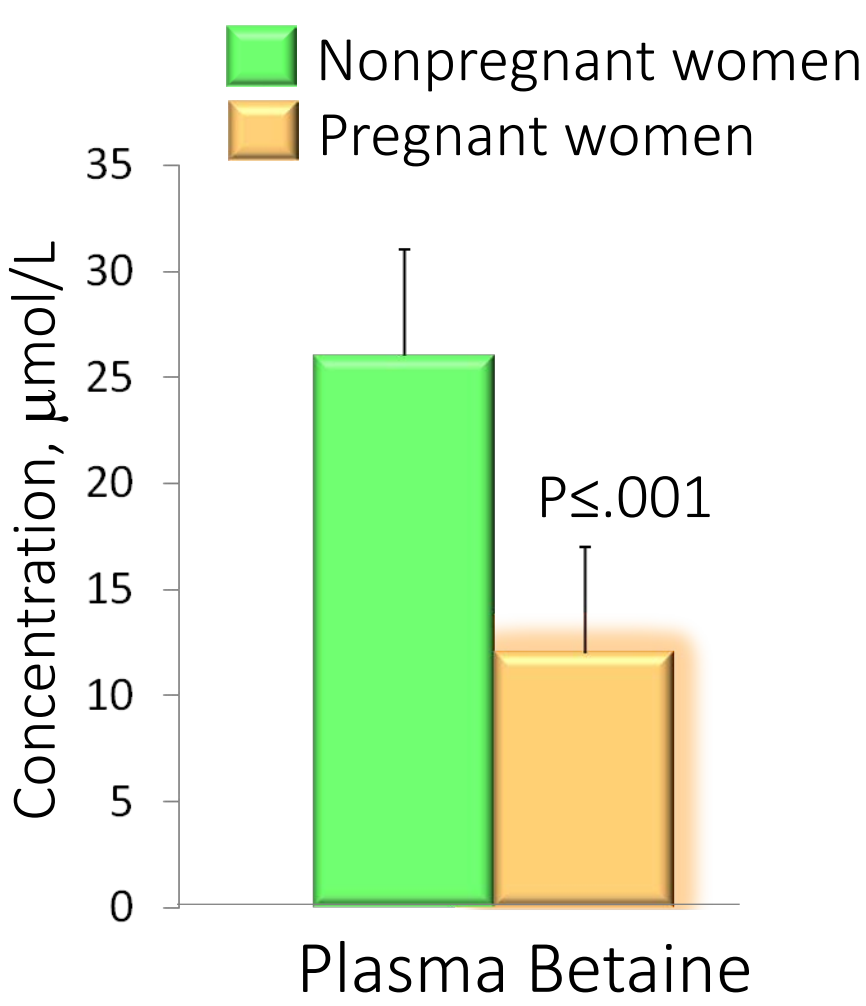
Cellular Function ← Proteins ← Gene Expression ← *Epigenetic modification of placental and fetal genomes*

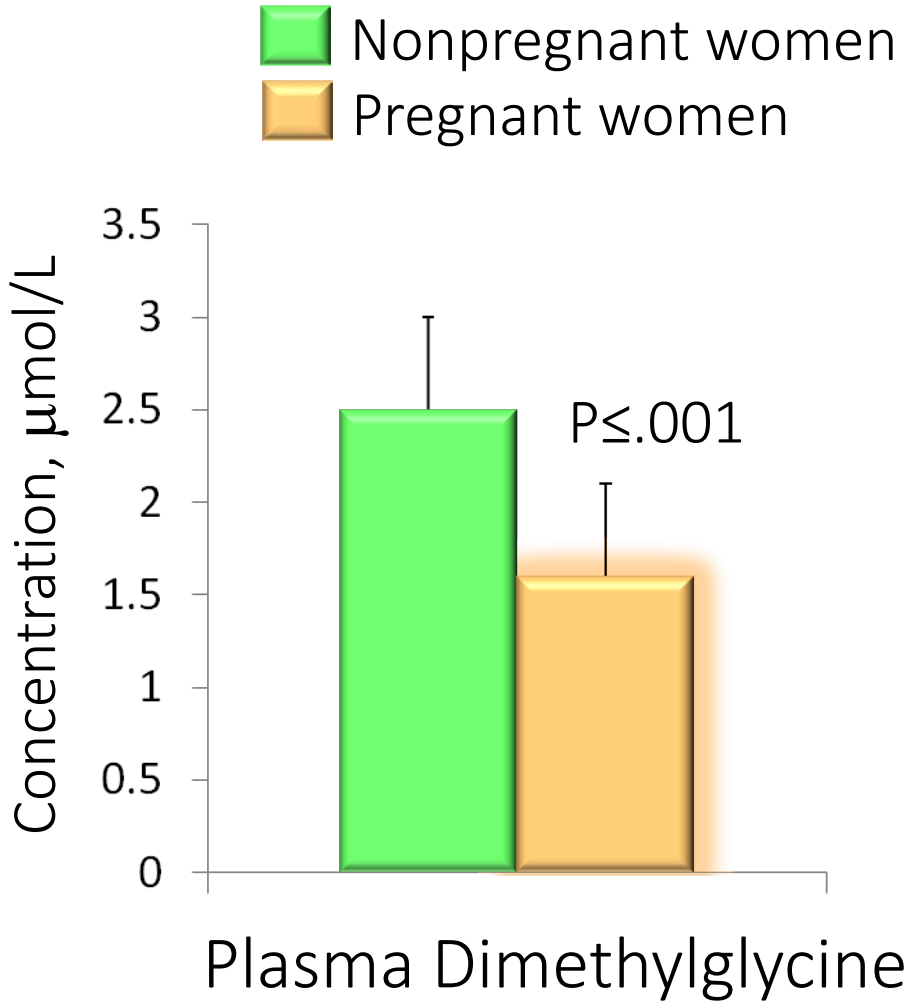
Cellular Function → Lasting Effects on Health

Demand For Choline Is Very High During Pregnancy


Choline
Betaine
MET
SAM
CDP-choline pathway
PEMT "de novo" pathway
PE (x3)
CDP-PC
16:0
PEMT-PC
DHA
Maternal liver
Maternal dietary choline
PC
VLDL
CM
Choline
PC
Baby derives choline from mother

Pregnancy Depletes Choline-Derived Methyl Donors

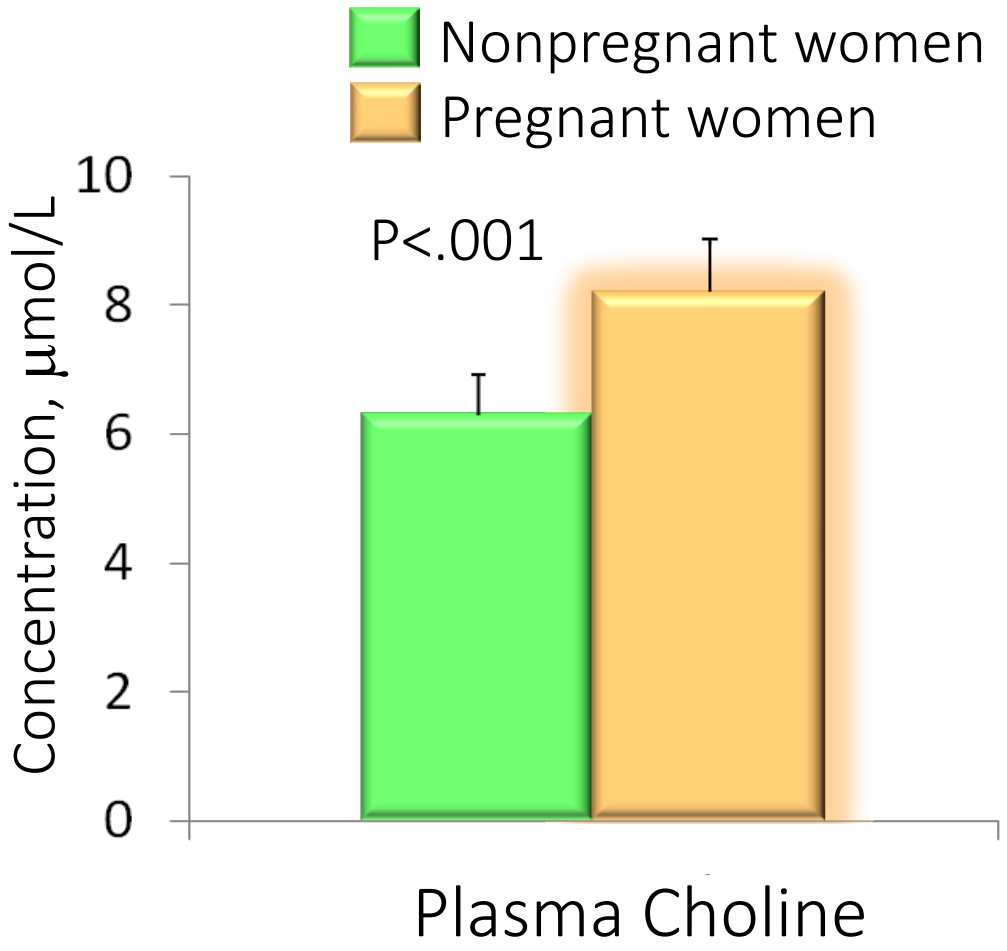


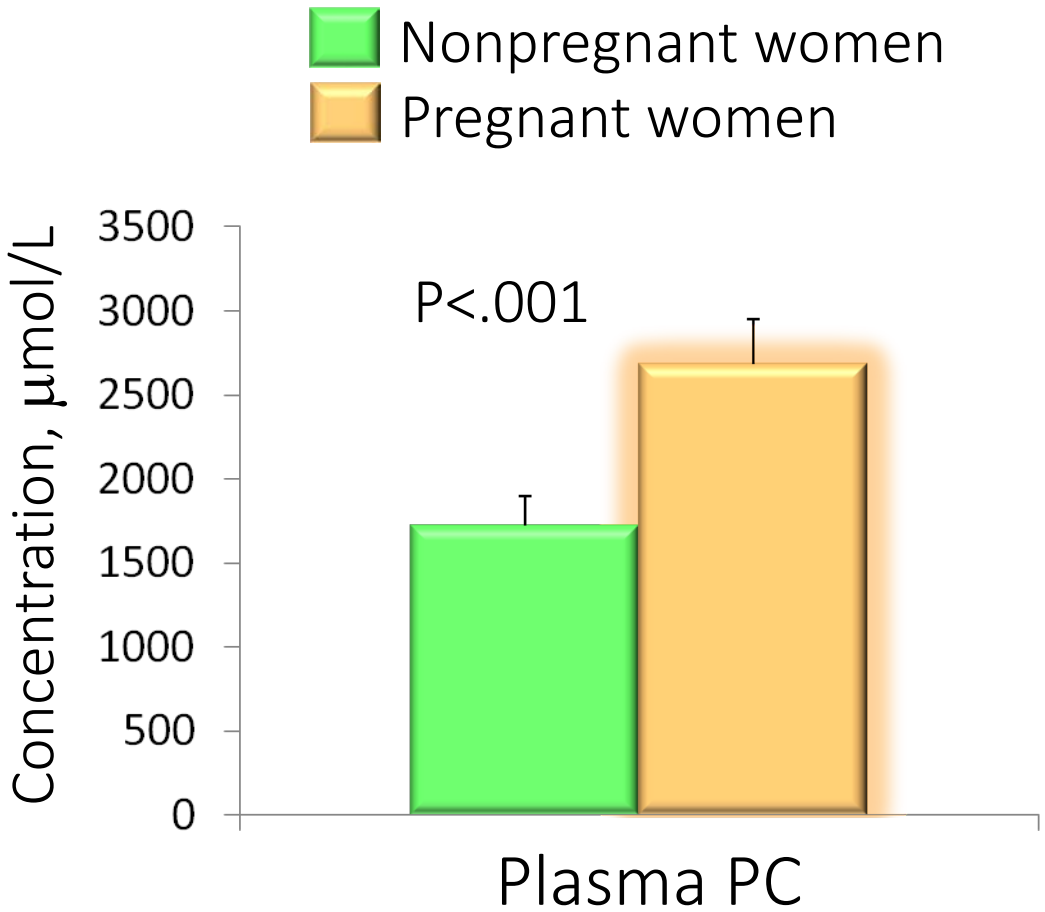


Pregnant (vs nonpregnant) women oxidize less choline to betaine, yet use more betaine and dimethylglycine as methyl-group (1-C) donors.

Yan et al. *Am J Clin Nutr*. 2012;95:1060-71
Yan et al. *Am J Clin Nutr*. 2013;98:1-9

Pregnancy Increases Circulating Choline and PC





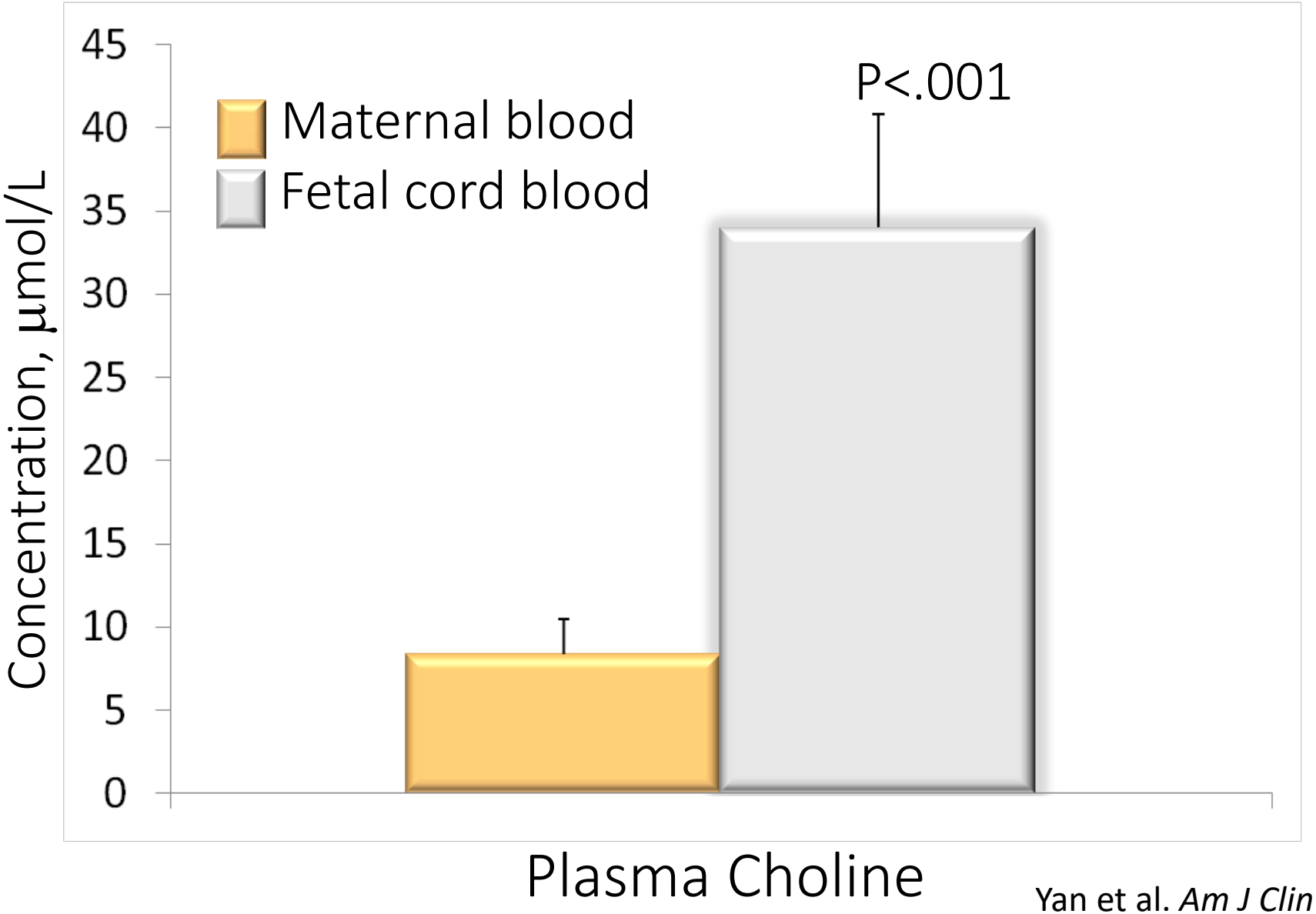
Pregnant (vs nonpregnant) women catabolize more of the endogenously made PC to choline

Pregnant (vs nonpregnant) women use more choline to synthesize PC through both the CDP-choline and PEMT pathways

Yan et al. *Am J Clin Nutr*. 2013;98:1-9

Yan et al. *Am J Clin Nutr*. 2012;95:1060-71

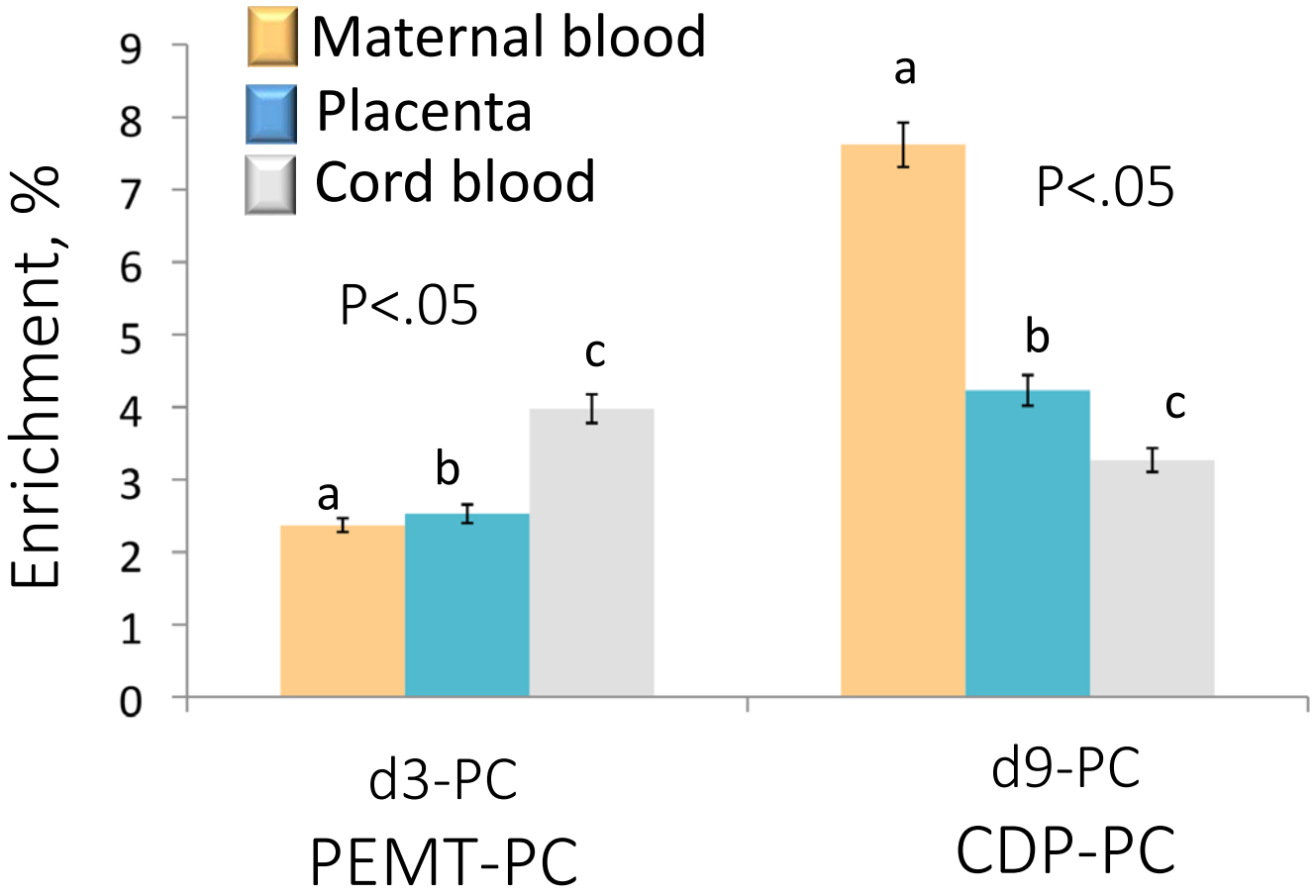
Large Amounts Of Choline Are Transferred To Baby

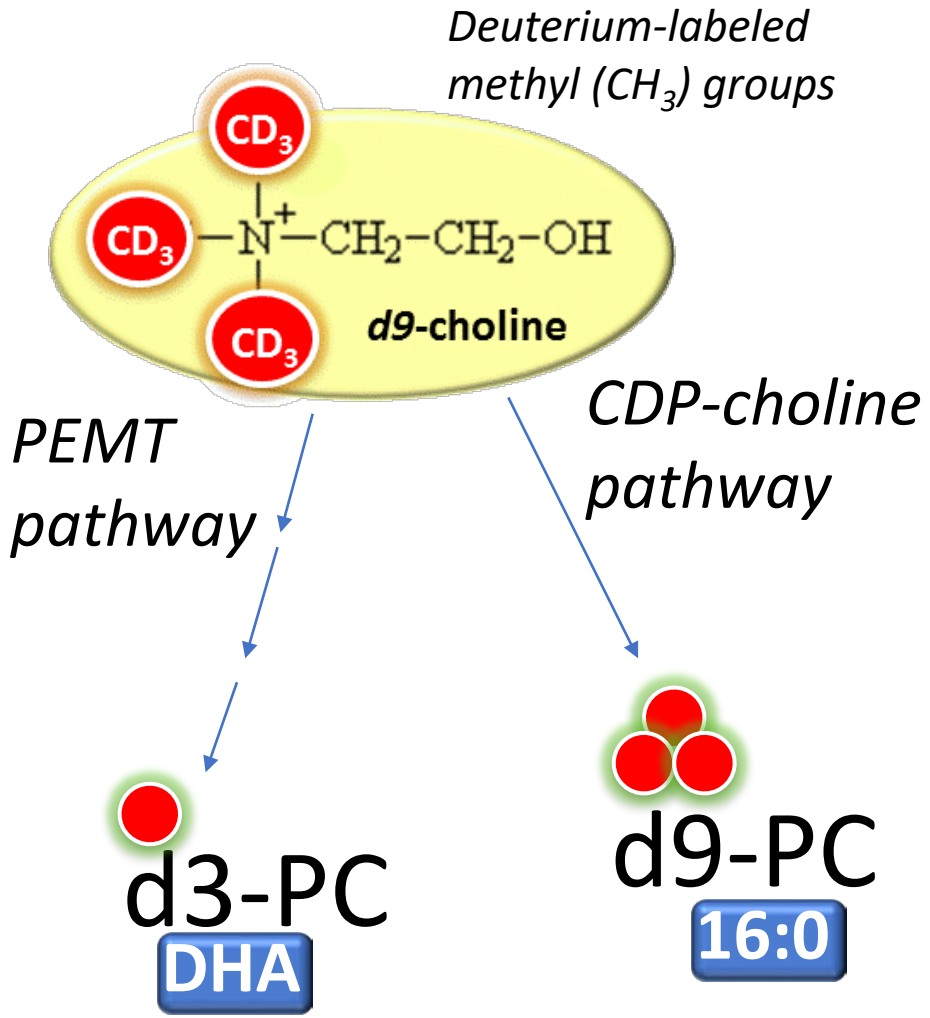


Yan et al. *Am J Clin Nutr*. 2012;95:1060-71

PEMT-PC Is Preferentially Transferred To Baby

12-week controlled feeding study using deuterium-labeled choline as a tracer

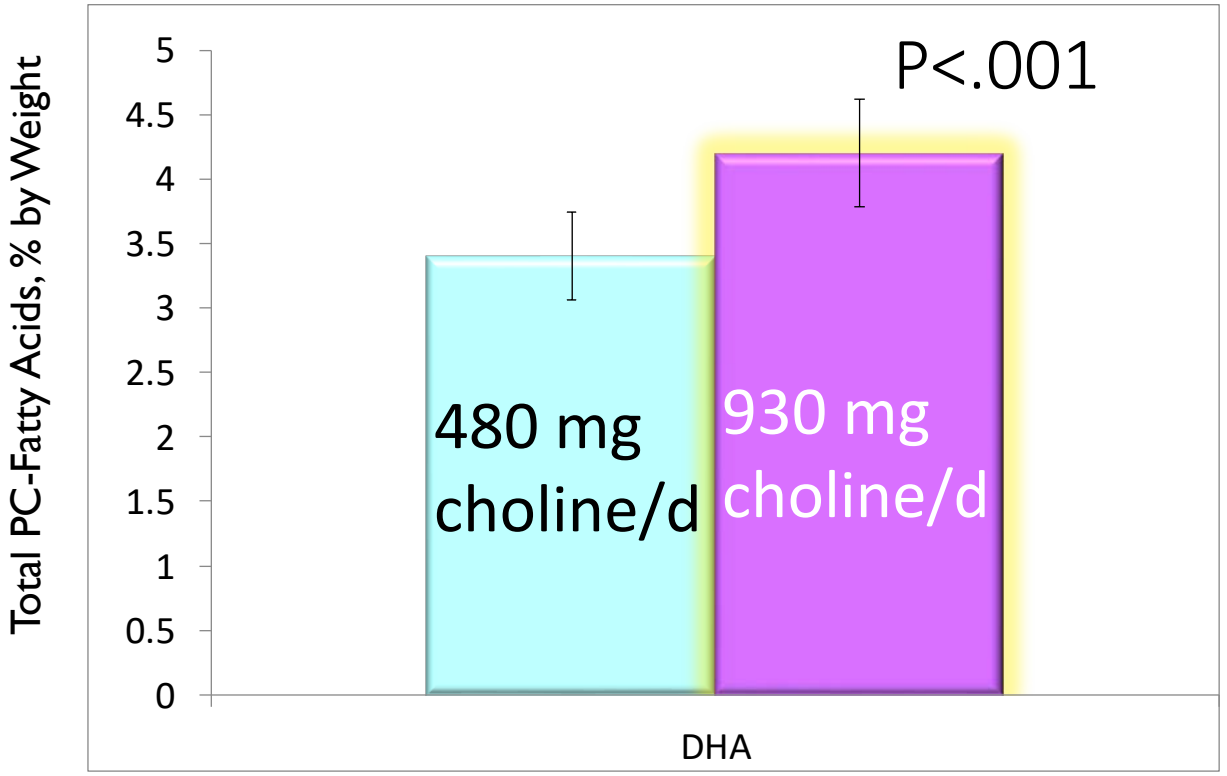




Unique requirement for PEMT-PC by the developing fetus

Yan et al. *Am J Clin Nutr*. 2013;98:1-9

Higher Choline Intake Enhances PEMT-PC Synthesis and DHA Status In Women of Reproductive Age



Circulating PC-DHA
Women of Reproductive Age

Supplementing with ~2X choline (930 vs 480 mg/d):

- Enhances PEMT activity and the export of DHA from liver
- Increases the amount of PC-DHA in RBCs, a biomarker of DHA status

Suggests giving additional choline across gestation may be a way to increase DHA supply to the fetus

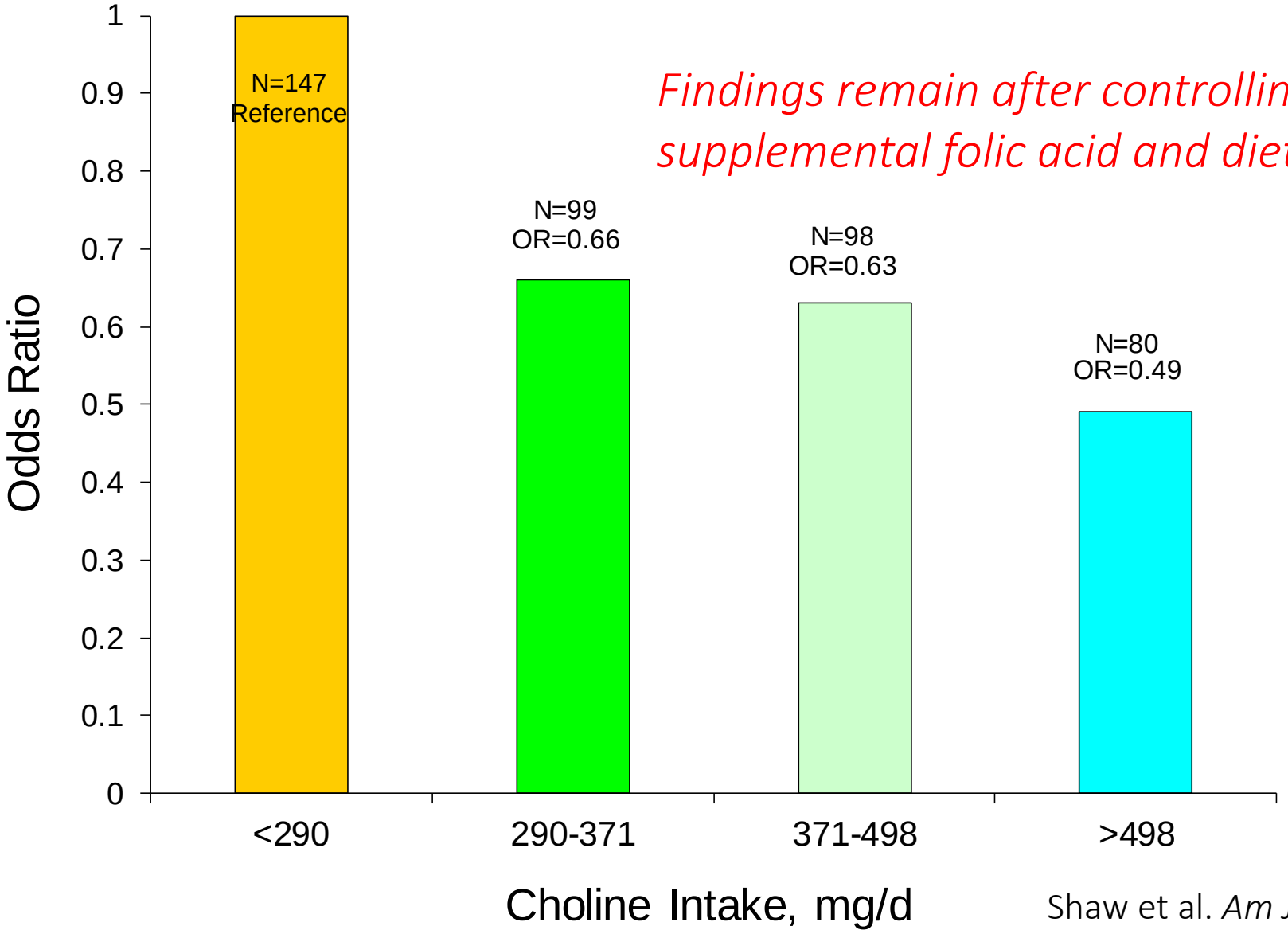
West AA, et al. *Am J Clin Nutr*. 2013;97:718-727.

Higher Choline Intake During Pregnancy:

- Increases circulating concentrations of choline-derived methyl donors, which are depleted *(Yan et al. Am J Clin Nutr. 2012;95:1060-71; Yan et al. Am J Clin Nutr. 2013;98:1-9)*
- Enhances DNA methylation of the placenta --> may beneficially influence genome stability and integrity *(Jiang et al. FASEB J. 2012;26:3563-3574)*
- Overcomes some of the metabolic disturbances in choline metabolism that arise from variants in both choline (eg., *PEMT*) and folate (eg., *MTHFR*) metabolizing genes (*Ganz et al. FASEB J. 2016 30, 3321–3333; Ganz et al. Int J Mol Sci. 2017;26;18(2)*

Higher Maternal Choline Intake Improves Pregnancy Outcomes

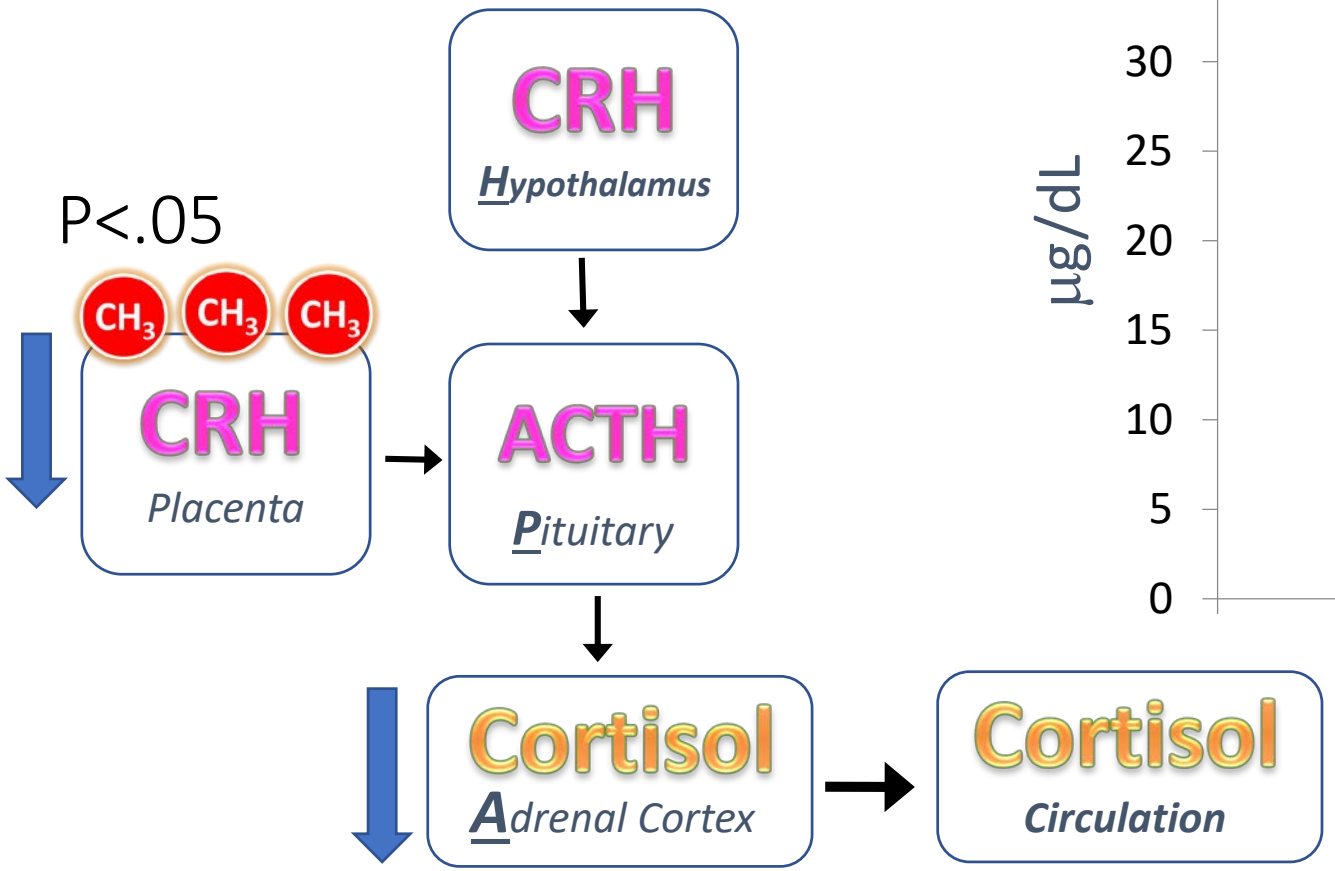
Higher Maternal Choline Intake Is Associated with Lower Neural Tube Defect Risk

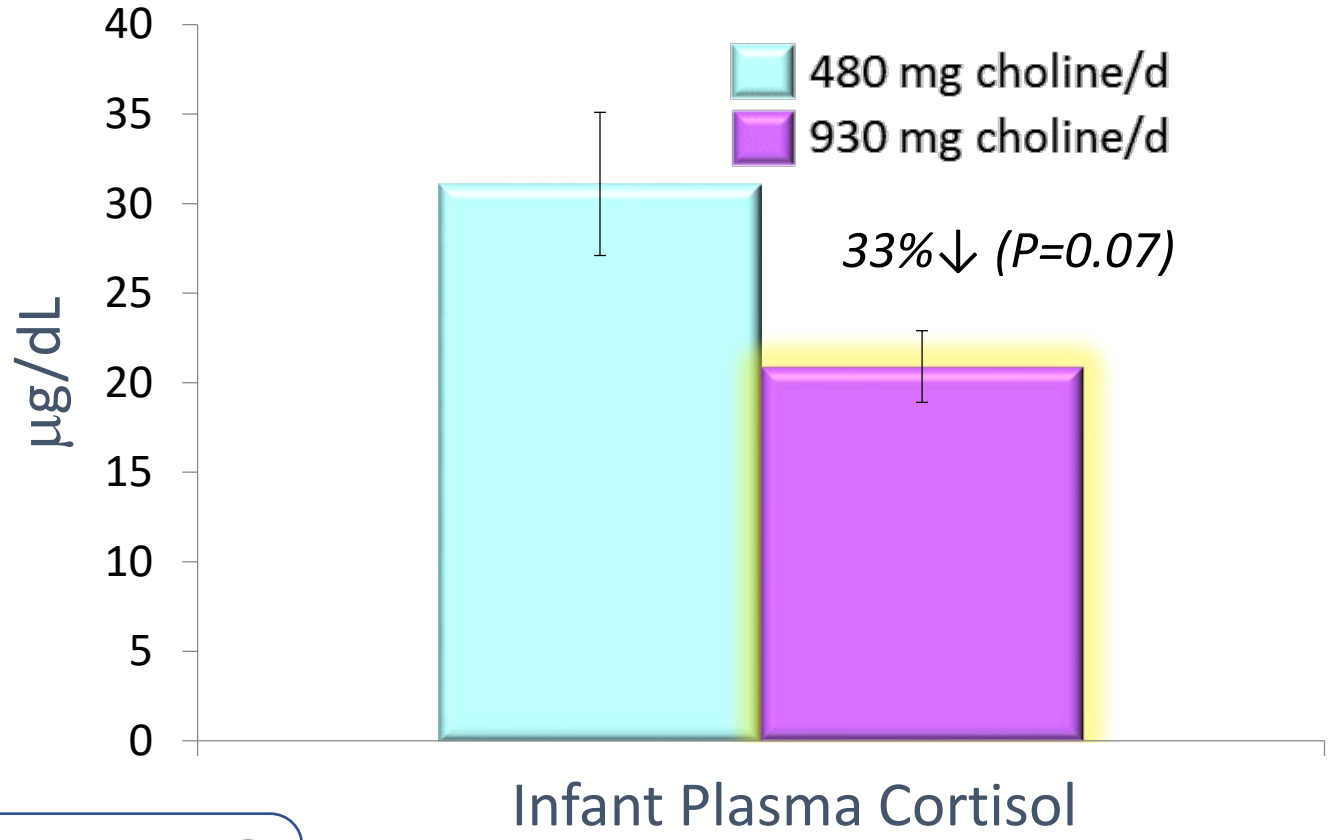


Findings remain after controlling for intakes of supplemental folic acid and dietary folate

Shaw et al. *Am J Epidemiol*. 2004;160:102-109.

Higher Maternal Choline Intake Eases Baby's Response to Stress





Jiang X, et al. *FASEB J.* 2012;26:3563-3574.

Less Stress Reactivity in "Choline" Babies May Decrease Vulnerability to Stress-Related Diseases and Improve Learning Outcomes

"Choline" Baby

Meaney et al. 2007. *Trends in Molecular Medicine*. 2007;13:269-277; National Scientific Council on the developing Child. http:www.developingchild.net

Offspring

CRH
H*ypothalamus*

ACTH
P*ituitary*

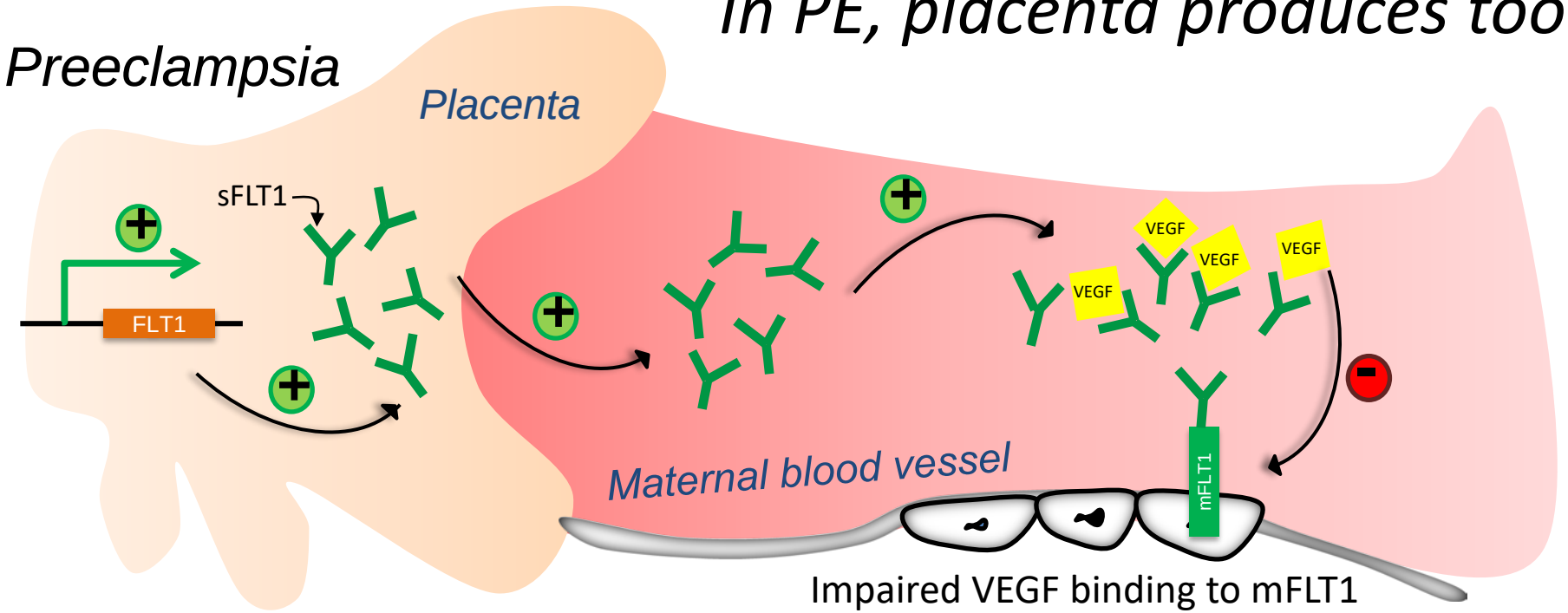
Cortisol
A*drenal Cortex*

- Hypertension
- Obesity
- Diabetes
- Depression

- Memory
- Learning
- Attention

Higher Maternal Choline Intake Lowers Preeclampsia Risk Factor, sFLT1

In PE, placenta produces too much sFLT1



Impaired VEGF binding to mFLT1

↓

Endothelial dysfunction

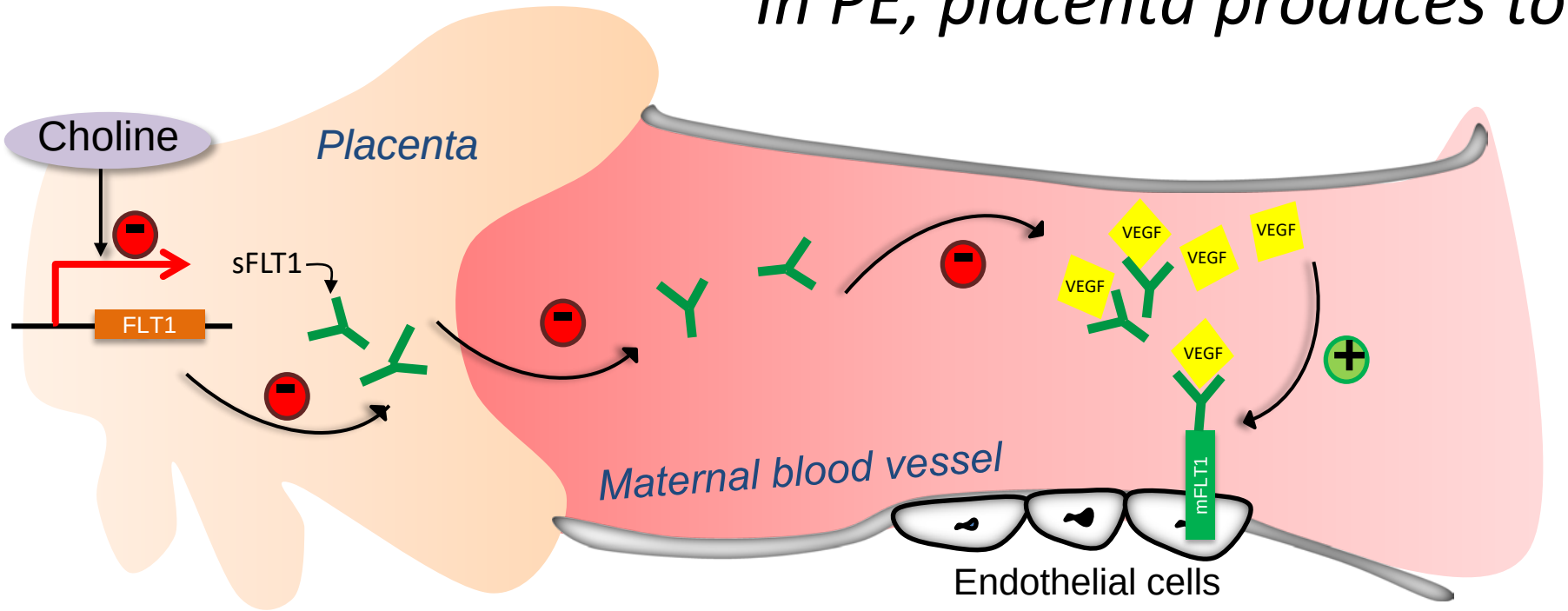
↓

Maternal hypertension
Maternal kidney dysfunction

Jiang et al. *FASEB J.* 2013;27:1245-1253.

Higher Maternal Choline Intake (930 vs. 480 mg/d) Lowers Preeclampsia Risk Factor, sFLT1

In PE, placenta produces too much sFLT1



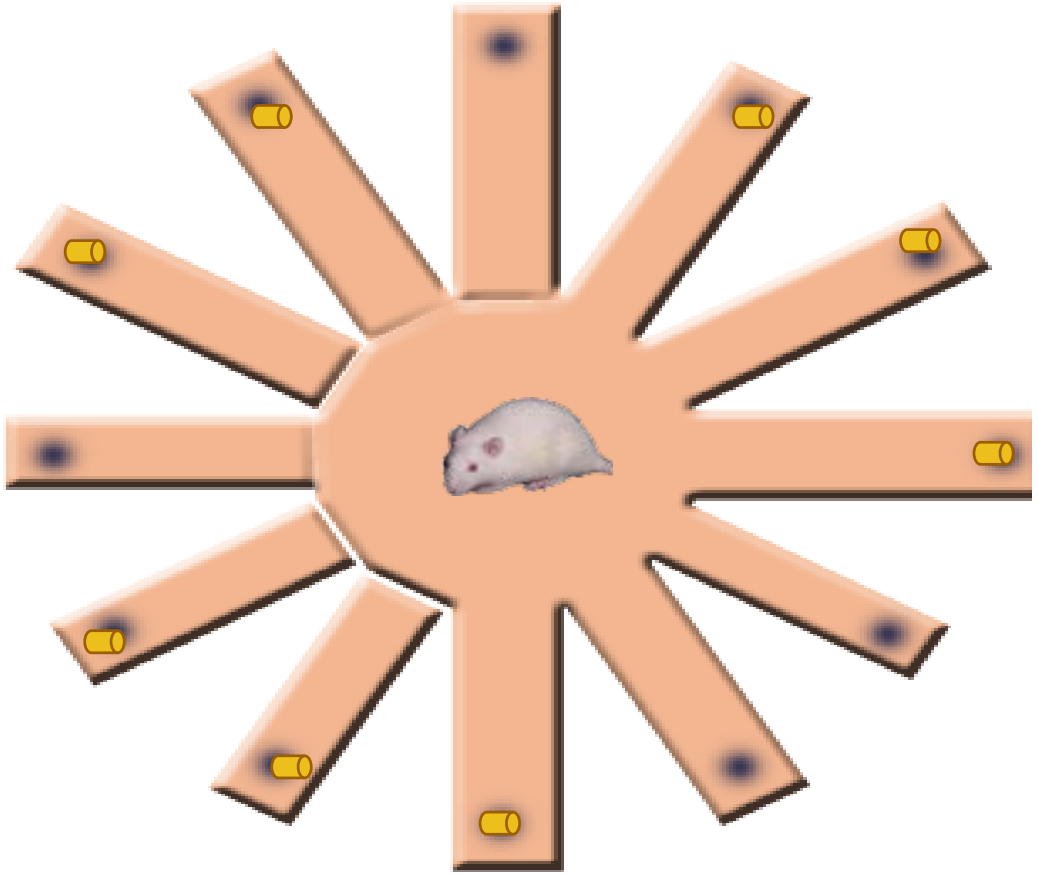
Normal VEGF binding to mFLT1

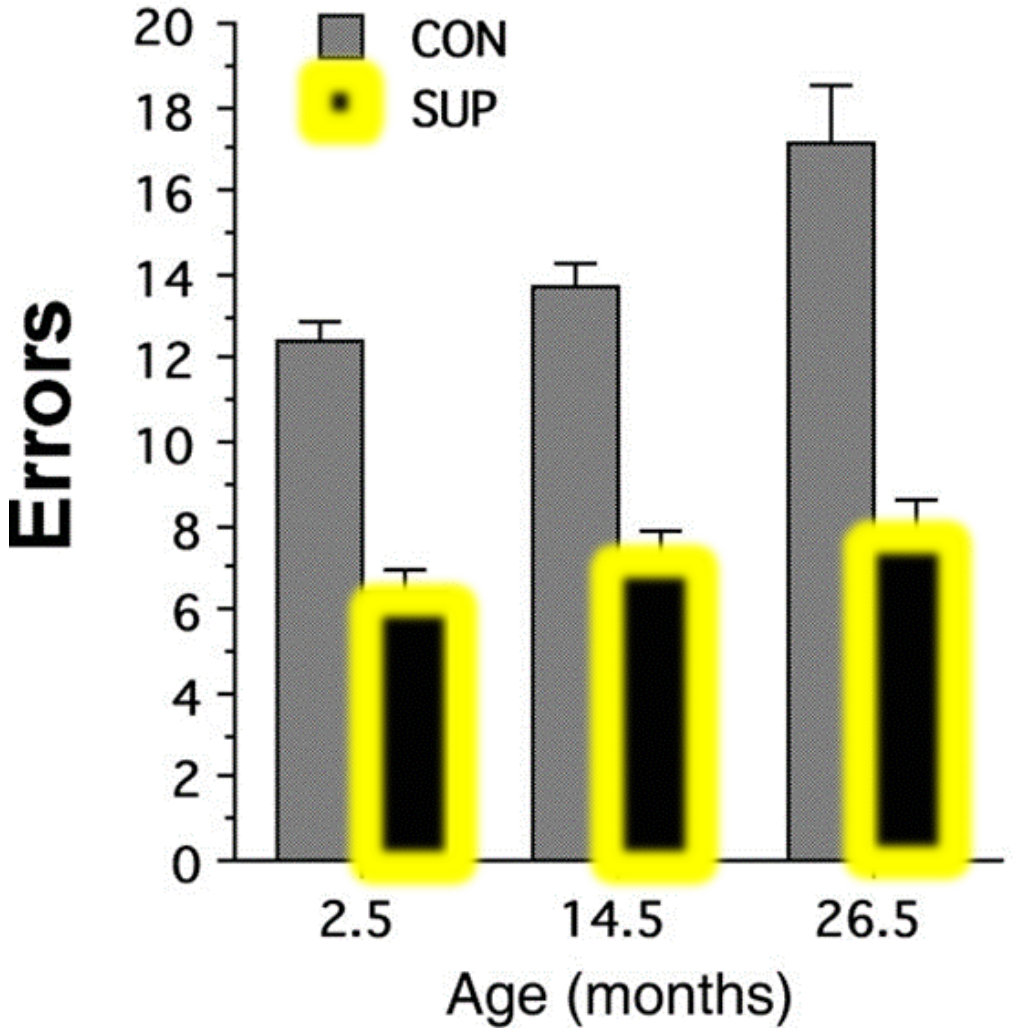
↓

Endothelial health

Jiang et al. *FASEB J.* 2013;27:1245-1253.

Higher Maternal Choline Intake Improves Offspring Cognitive Functioning (rodents)





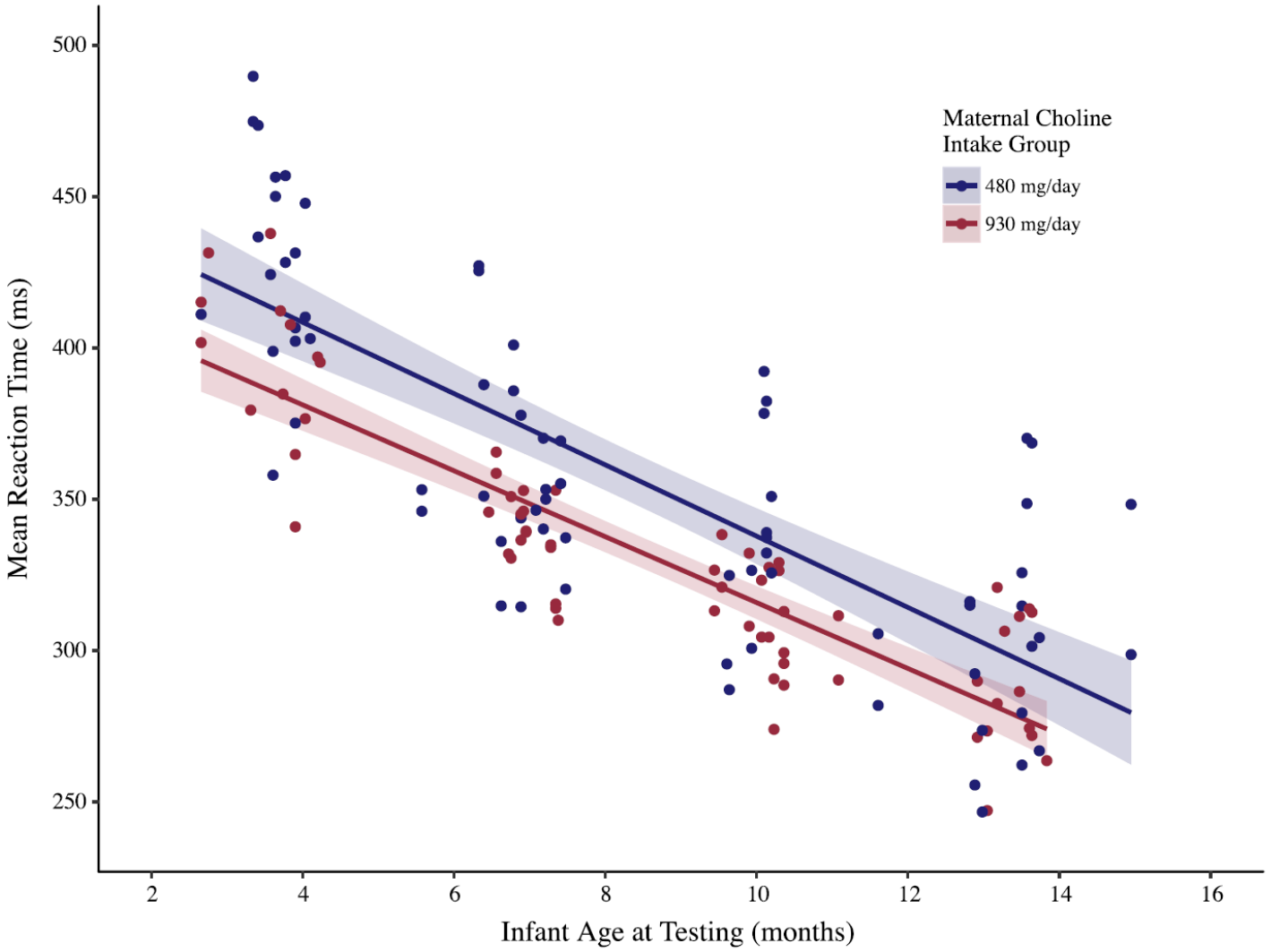
CON = control; SUP = supplementation.

Meck WH, Williams CL. *Neurosci Biobehav Rev.* 2003;27:385-399.

Rodent studies have also shown that prenatal choline protects the offspring brain from a wide variety of neural insults including *Alzheimer's disease*, *fetal alcohol syndrome*, *autism*, *Down syndrome*, and *early-life iron deficiency* *(reviewed in Nutrients 2019, 11, 1823)*

Higher Maternal Choline Intake (930 vs. 480 mg/d) Improves Infant Information Processing Speed

Information Processing Speed



Administered a visual attention task to measure eye movement reaction time to sequences of briefly presented visual stimuli

Caudill et al. *FASEB J*. 2018;32:2172-2180

Cognitive Assessment in these Children at Age 7 Reveal Lasting Benefits of the Higher Maternal Choline Intake

- Attention
- Visual Memory
- Problem Solving

Bahnfleth et al. *Curr Dev Nutr* **2019,** *3* (Suppl 1).
Bahnfleth et al. *ASN 2018* Abstract Submission ID: 424013

Consistent with findings in the animal literature and with the Project Viva study (a large prospective cohort study), which reported better visual memory in 7-year-old children of mothers with highest (versus lowest) interquartile dietary choline intake during pregnancy (Am. J. Epidemiol. 2013;177:1338–1347)

Beneficial Effects of Higher Maternal Choline on Offspring Cognition Have Been Found in Other RCTs

- Improved attentional development among 5-week-old infants (Ross et al. 2013; Am. J. Psychiatry. 2013;170:290–298)
- Reduced attentional problems and social withdrawal in young children (Ross et al. 2016; Am. J. Psychiatry. 2016;173:509–516)
- Higher novelty preference scores in one-year-old children of alcoholic mothers (Jacobson et al. 2018; Alcohol Clin. Exp. Res. 2018;42:1327–1341)

Most Pregnant Women Do Not Meet Choline Intake Targets

Only 8% of US Pregnant Women Are Meeting The Choline AI

Population and Age	Adequate Intake	Tolerable Upper Limit (UL)
Infants, mo		
0–6	125 mg/d, 18 mg/kg	Not possible to establish
6–12	150 mg/d	Not possible to establish
Children, y		
1–3	200 mg/d	1,000 mg/d
4–8	250 mg/d	1,000 mg/d
9–13	375 mg/d	2,000 mg/d
Men, y		
14–18	550 mg/d	3,000 mg/d
≥19	550 mg/d	3,500 mg/d
Women, y		
14–18	400 mg/d	3,000 mg/d
≥19	425 mg/d	3,500 mg/d
Pregnant	450 mg/d	Age-appropriate UL
Lactating	550 mg/d	Age-appropriate UL

Data from the Institute of Medicine, National Academy of Sciences.[11]

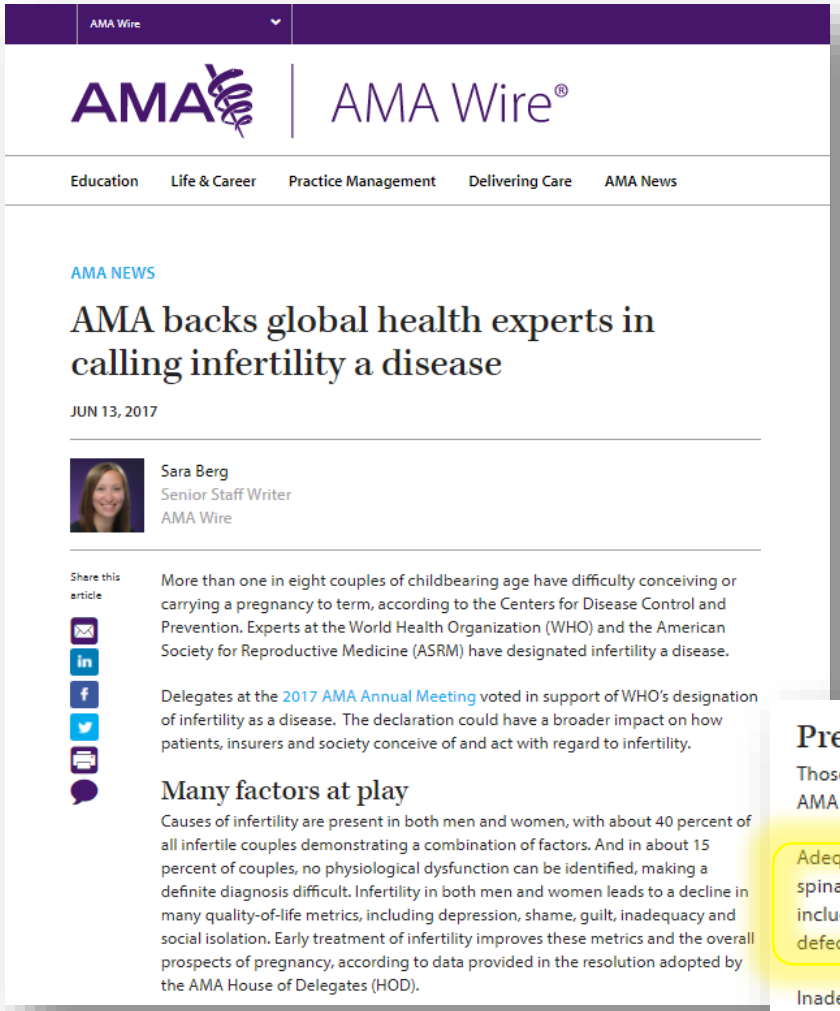
- Choline AI is 450 mg/d
- Average choline intake is ~322 mg/d
- Choline gap is increased further by common genetic variants that increase choline requirements

References: *Nutrients 2017, 9, 839*; *Nutrients* 2019 11, 1823; *FASEB J* 2016;30, 3321-3333; *Int J Mol Sci.* 2017 26;18(2); JAMA Netw Open. 2019;2(6):e195967

None of the top 25 prenatal vitamins contain the recommended amount of choline

J Fam Med Dis Prev 2016, 2:048
Volume 2 | Issue 4

Most (17 of 25) don't contain any choline



AMA Wire

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AMA NEWS

AMA backs global health experts in calling infertility a disease

JUN 13, 2017

Sara Berg
Senior Staff Writer
AMA Wire

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More than one in eight couples of childbearing age have difficulty conceiving or carrying a pregnancy to term, according to the Centers for Disease Control and Prevention. Experts at the World Health Organization (WHO) and the American Society for Reproductive Medicine (ASRM) have designated infertility a disease.

Delegates at the 2017 AMA Annual Meeting voted in support of WHO's designation of infertility as a disease. The declaration could have a broader impact on how patients, insurers and society conceive of and act with regard to infertility.

Many factors at play

Causes of infertility are present in both men and women, with about 40 percent of all infertile couples demonstrating a combination of factors. And in about 15 percent of couples, no physiological dysfunction can be identified, making a definite diagnosis difficult. Infertility in both men and women leads to a decline in many quality-of-life metrics, including depression, shame, guilt, inadequacy and social isolation. Early treatment of infertility improves these metrics and the overall prospects of pregnancy, according to data provided in the resolution adopted by the AMA House of Delegates (HOD).

Prenatal supplementation

Those patients who do conceive, by any method, now have new advice from the AMA on proper prenatal vitamin supplementation.

Adequate levels of choline—an important nutrient that helps a baby's brain and spinal cord to develop properly—are necessary to maintain normal pregnancy including neural development of the fetus and reducing the incidence of birth defects.

Inadequate choline levels during pregnancy are thought to negatively affect cognitive development. Neural tube and hippocampus development also are dependent on adequate choline intake.

Prenatal vitamins only contain 0–55 mg of choline, leaving the majority of pregnant and lactating women without enough dietary choline to protect the health and development of their babies, according to data cited in a resolution adopted by the HOD.

Delegates voted to support evidence-based amounts of choline in all prenatal vitamins.

Read more news coverage from the 2017 AMA Annual Meeting.

In 2017, **The American Medical Association** (AMA) passed a resolution supporting actions to boost ***choline*** amounts in all prenatal vitamins

POLICY STATEMENT

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

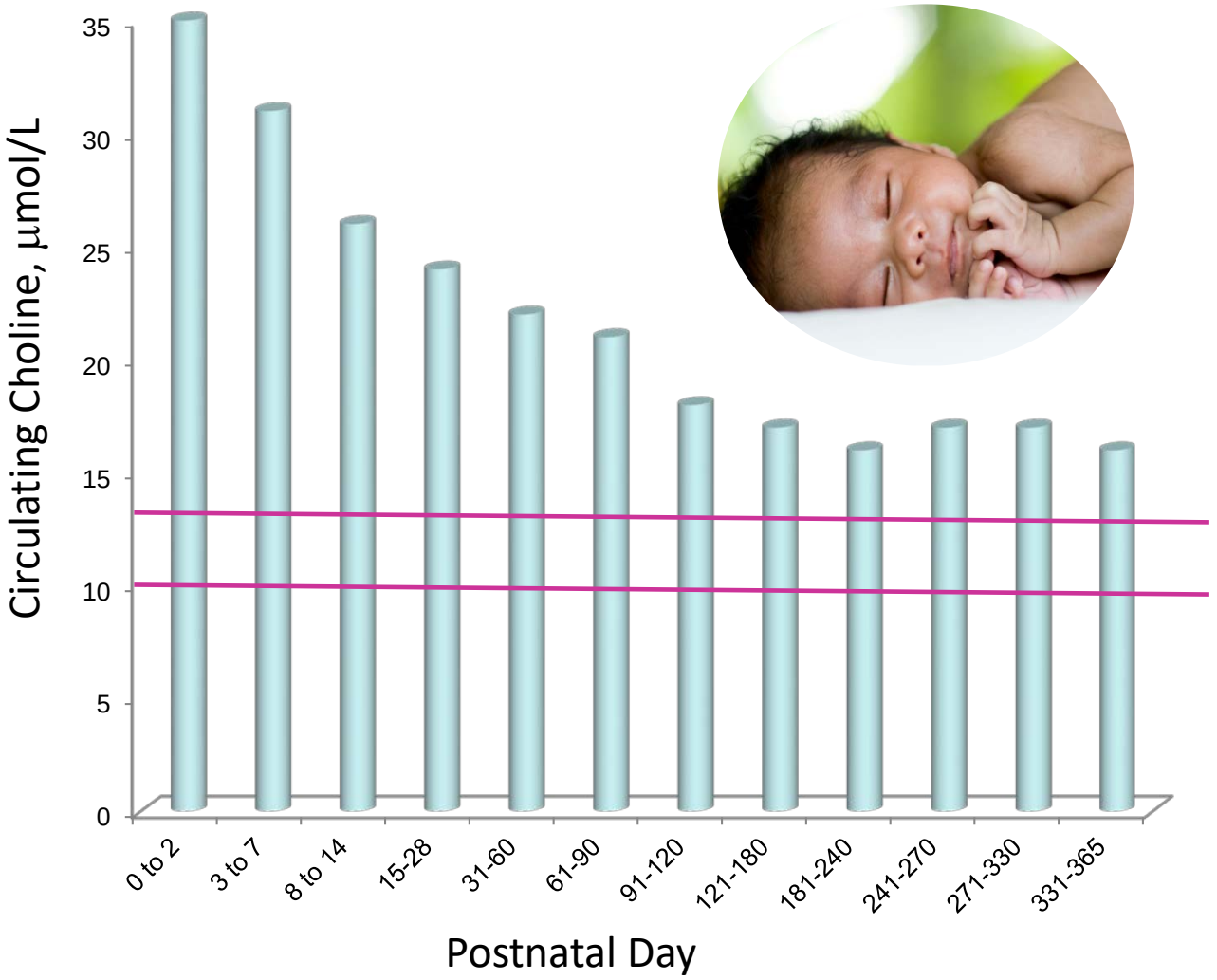
The American Academy of Pediatrics recently recognized ***choline*** as a key nutrient to support neurodevelopment during the first 1000 days

Called upon healthcare providers to ensure pregnant women and young children have adequate choline intakes

PEDIATRICS Volume 141, 2018

High Demand for Choline Continues in the Postnatal Period

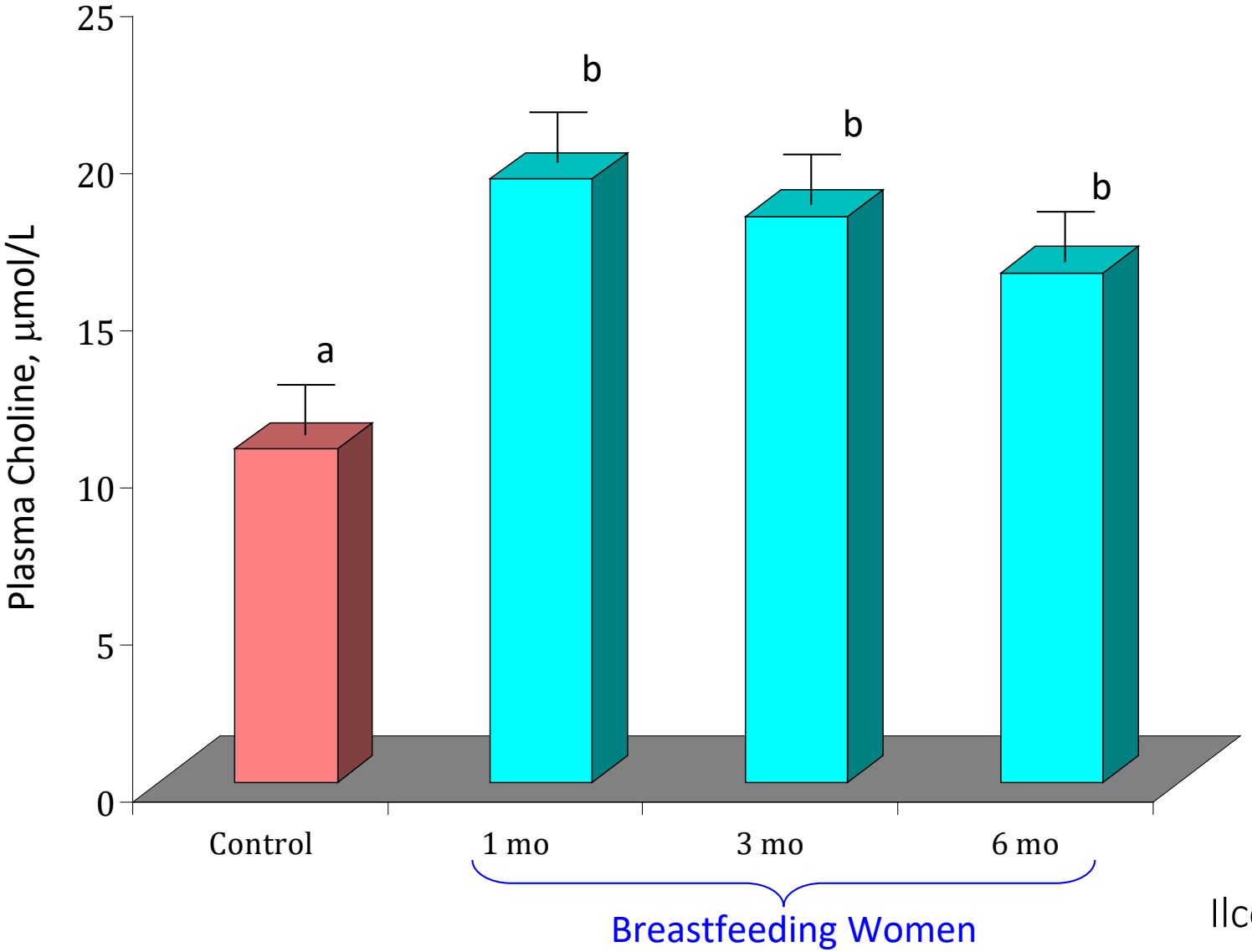
Circulating Choline Remains Elevated Throughout the First Postnatal Year



Facilitates transfer of choline across the blood-brain barrier (best when choline levels are >14 µmol/L)

Ilcol YO, et al. *J Nutr Biochem*. 2005;16:489-499; Wurtman RJ. *Trends Neurosci.* 1992;15:117-122; Klein J, Koppen A, Loffelholz K. *J Neurochem*. 1990;55:1231-1236.

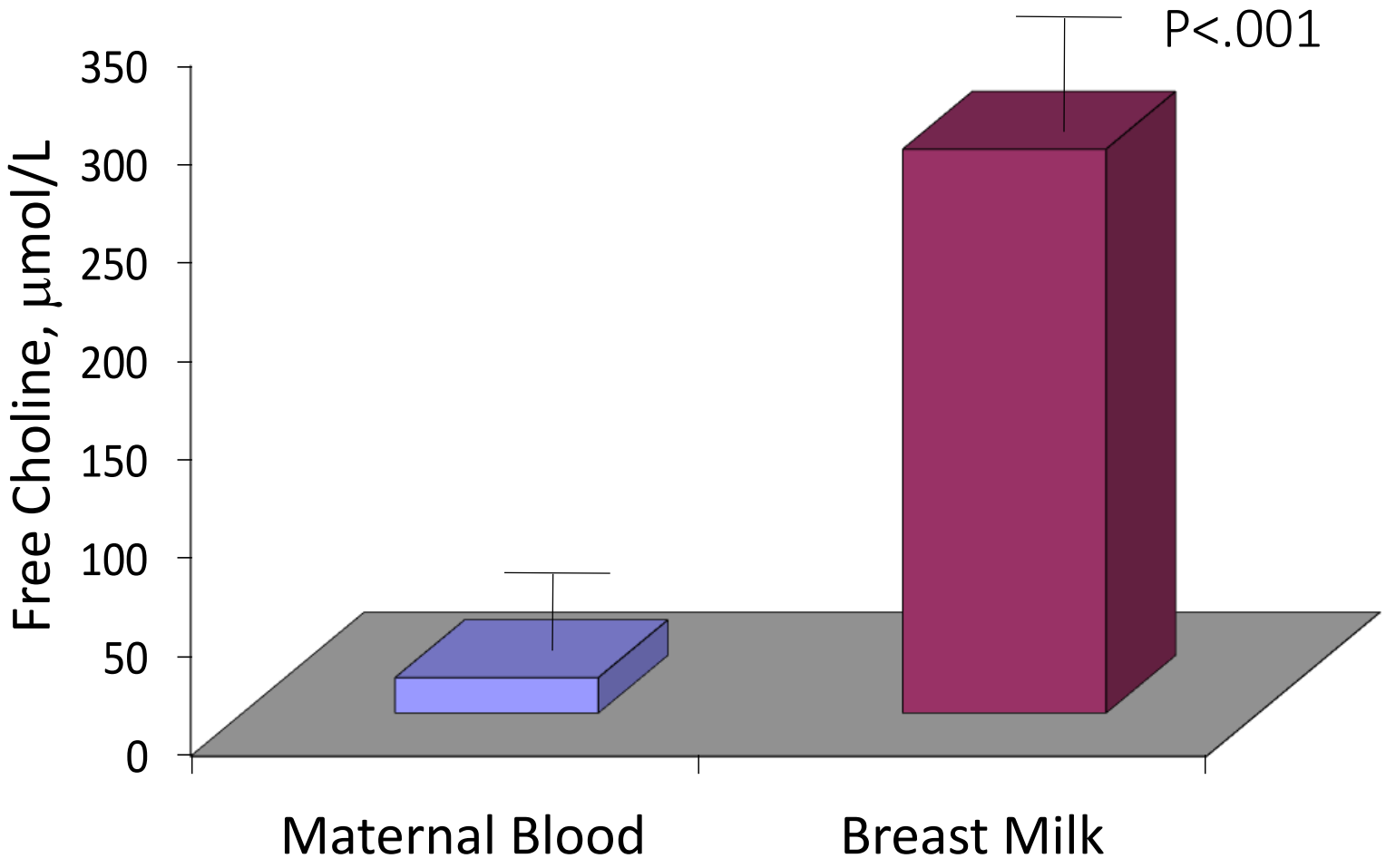
Circulating Choline Remains Elevated in Lactating Moms



Facilitates uptake of choline by the mammary epithelium

Ilcol YO, et al. *J Nutr Biochem*. 2005;16:489-499

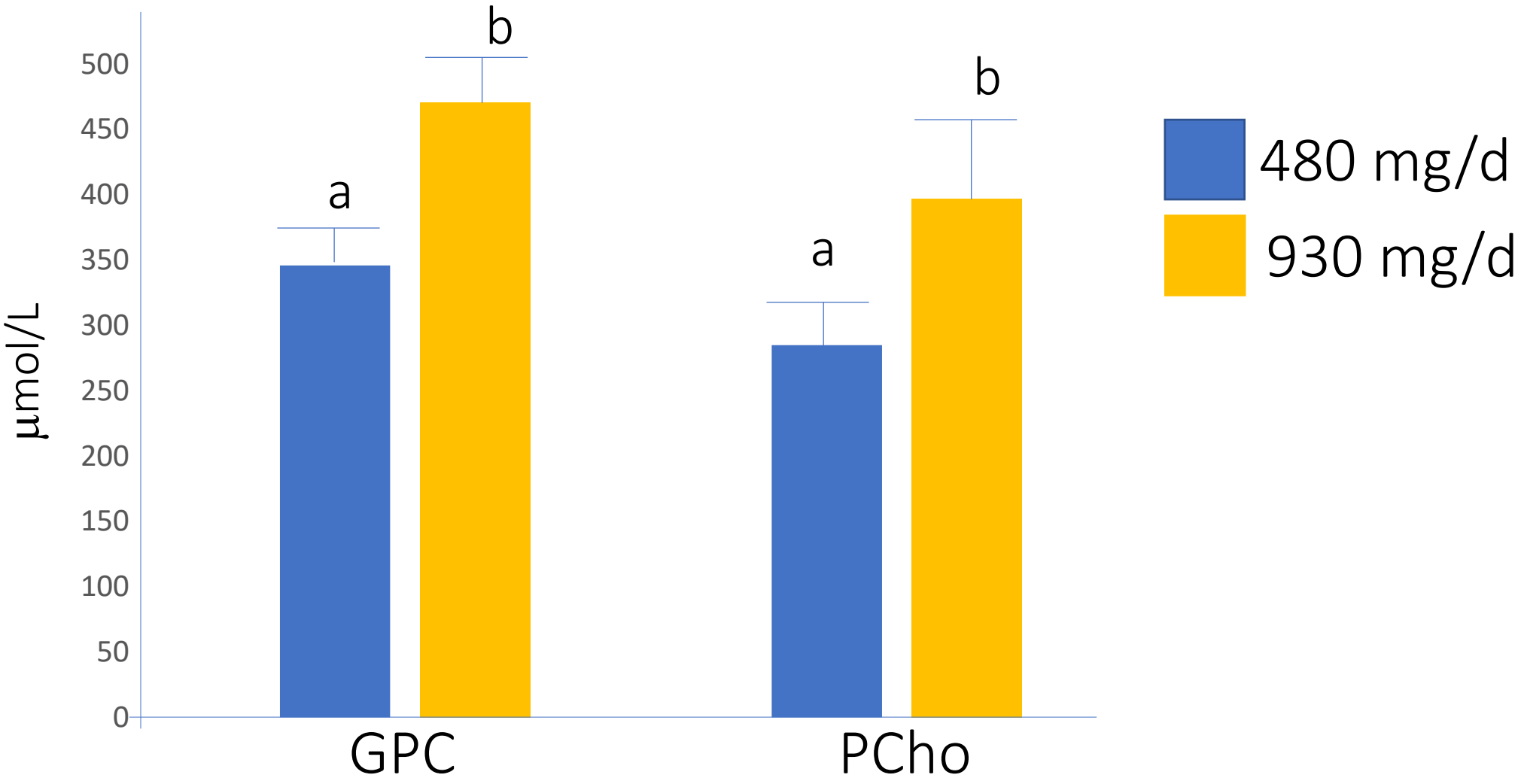
Large Amounts of Choline Are Present in Human Milk



Breast Milk Choline Content Is ~15 Times Higher Than Maternal Blood Levels

Ilcol YO, et al. J Nutr Biochem. 2005;16:489-499.

Breastmilk Choline Content Can Be Improved With A Higher Maternal Choline Intake



Davenport et al. *J Nutr Biochem*. 2015;26:903-11

Key Takeaways

- Large amounts of choline are required during and after pregnancy for normal fetal and neonatal development.
- Higher maternal choline intake will likely improve pregnancy outcomes and offspring neurocognitive health.
- Most pregnant (and lactating) women need to increase dietary choline intake or consume a choline supplement to meet recommendations.