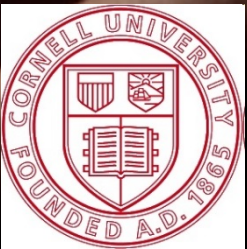




Iron, Vitamin D and Calcium: New Evidence During Pregnancy and Lactation

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Iron

1. What data are available to support the efficacy of typical Fe supplementation doses?
2. Are lower iron supplementation doses efficacious?
3. Are the Hb thresholds established in the 1970's still applicable?
4. Are there groups at higher risk of Fe insufficiency / excess?

Vitamin D

1. Is vitamin D insufficiency really a problem for pregnant / lactating women?
2. How much D should women be consuming and what is the evidence to support this?

Calcium

1. Are calcium recommendations appropriate for pregnant/lactating women given the results of randomized controlled trials over the past 30 years?
2. What do we know now that we didn't know 30 years ago?
3. Are there any groups at elevated risk of insufficiency?

2001 DRI for Fe During Pregnancy / Lactation



	Female		Pregnancy			Lactation		
	Age	EAR / RDA	EAR	RDA	UL	EAR	RDA	UL
Iron 2001	14-18 y	7.9 / 15 mg	23	27	45	7	10	45
	19-50 y	8.1 / 18 mg	22	27	45	6.5	9	45

Increase during pregnancy:

- Factorial modeling to meet marked increase in gestational Fe demands
- US prenatal contains 27 mg Fe/ Health Canada recommends 16-20 mg Fe

Decrease during lactation:

- Net savings if exclusively breast feed and have physiological amenorrhea

Efficacy of Prenatal Fe Supplementation?

- USPSTF (2015): “Evidence supports the effectiveness of routine Fe supplementation during pregnancy for improving maternal hematological indexes, but the clinical significance for both pregnant women and infants remains unclear” (McDonagh, AHRQ 2015)
- Cochrane: Maternal Fe supplementation (35 trials; Fe vs no Fe or placebo) reduces the risk of maternal anemia and ID in pregnancy, effect on other outcomes less clear (Pena-Rosas, 2015, 2012)
- 2016 NIH / ODS workshop on Fe screening and supplementation in Fe replete pregnant women to review this literature and identify research needs (Am J Clin Nutr 2017; 106;Suppl)
- The form of supplement most often tested (sulfate) is not the form used in commercial products (typically fumarate or gluconate) (Saldana, J Nutr 2019)
- Highlights the need for more research to inform policy and practice decisions

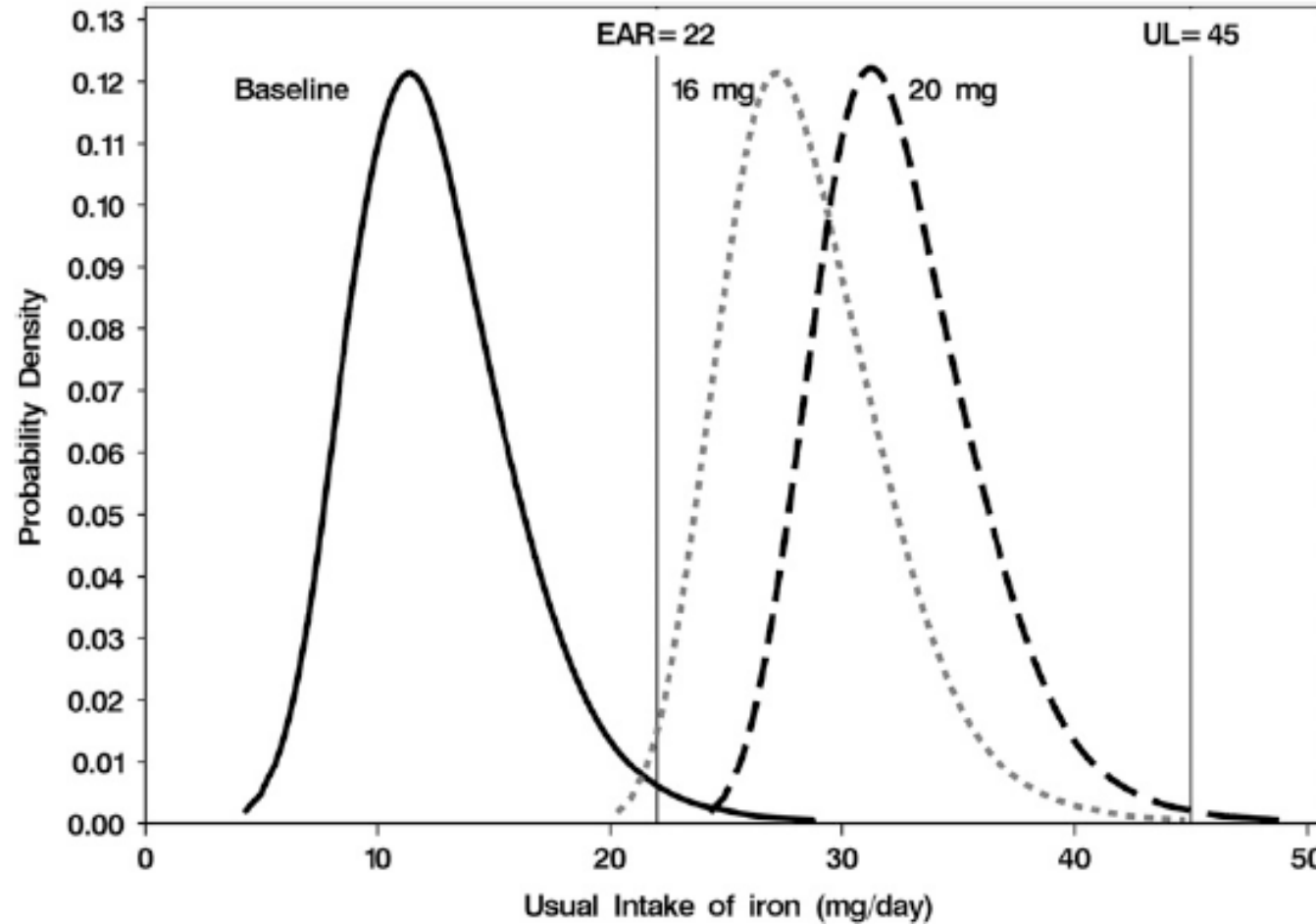
Gestational Anemia and ID in North America

Study Population	Iron Status Variable	Trimester, % (n)		
		1	2	3
NHANES 1999-2010 (12-49 y) (Mei, 2011)	ID: SF<12 ug/L	7.3 (189)	23.7 (416)	39.2 (384)
	Anemia	2.7 (189)	2.2 (416)	10.8 (384)
NHANES 1999-2010 (12-49 y) (Gupta, AJCN, 2017)	ID: TBI < 0 mg/kg	5.3 (210)	12.7 (447)	27.5 (414)
	IDA		2.6% (1.3%, 4.0%)	
Canada-APrON (16-40 y) (Unpublished data) R Bell	ID; SF < 12 ug/L	3 (286)	10 (1020)	40 (847)
	Anemia	2 (540)	2 (1894)	5 (1673)

Gestational Adaptations in Fe Homeostasis

- Non-heme Fe absorption increases as Fe stores are depleted; 3% increase per 10 ug/L decrease in SF (O'Brien, AJCN 1999)
- Erythropoietin (EPO), hepcidin and erythroferrone help maintain maternal Fe homeostasis;
 - EPO: significantly increases as Fe stores are depleted (Ru, AJCN 2016, Lee, J Nutr 2014)
 - Hepcidin: decreases as Fe stores depleted, impacted by inflammation (Lee, J Nutr 2014)
 - Erythroferrone: no human data at present
- The human placenta can upregulate Fe uptake proteins (TfR) in response to maternal Fe (Young, Placenta 2010), but the placenta may prioritize Fe for placental Fe demands over fetal Fe demands (Nemeth, JCI, 2019)
- If maternal Fe physiology can respond to decreased maternal iron stores, might lower prenatal Fe doses be efficacious?

Are Lower Prenatal Fe Doses Adequate?



Cockell KA, AJCN 2009; 90:1023-8

- Canadian Community Health Survey (2.2);
 - 148 recalls in pregnant women
 - 4540 recalls, NP women
- Intake data from non-pregnant women used to estimate distributions of usual intake
- Typical dietary Fe intakes fell below the EAR for pregnancy
- 16 mg/d of supplemental Fe would be safe and adequate for pregnant women in Canada, prevalence of inadequate intakes would fall to <3%

Sources of Iron in the Diet

- Dietary Fe is consumed as non-heme Fe (~90%) and heme Fe (~10%)
- DRI estimated heme absorption averages 25%
- Using stable Fe isotopes and an intrinsically labeled meat (pork), we found pregnant women absorb 50% of heme Fe (Young et al., J Nutr 2010)
- Hepcidin was significantly associated with non-heme Fe absorption but was not associated with heme Fe absorption (Young et al., J Nutr 2010)
- Heme Fe absorption was not affected by maternal Fe status and did not differ between pregnant and non-pregnant women (Young et al., J Nutr 2010)
- It is important to consider both the quantity and the composition of Fe in the diet when evaluating dietary exposures of iron
- Variability in the Fe composition of the habitual diet may also influence interpretation of data from Fe supplementation studies

Supplemental Fe Dose and Absorption

- Baseline Fe status impacts response to Fe supplementation
- Anemic pregnant women may be advised to ingest 40 – 200 mg of Fe
- Percent absorption of non-heme Fe decreases as the Fe dose increases
- When high Fe loads are given orally, much of the Fe will not be absorbed, cost to benefit ratio?
- Large amounts of unabsorbed Fe may lead to dysbiotic effects on the gut microbiome
- Excessive supplemental Fe may increase risk of GI side effects (constipation, dark colored stools, nausea)

Hemoglobin Thresholds During Pregnancy

Agency	Anemia Definition	Notes
Centers for Disease Control (1989)	T1: Hb < 11.0 g/dL T2: Hb < 10.5 g/dL T3: Hb < 11.0 g/dL	-0.8 g/dL; Black adults -0.4 g/dL; Black <5 y
American Congress of Obstetricians and Gynecologists (2008)	T1: Hb < 11.0 g/dL T2: Hb < 10.5 g/dL T3: Hb < 11.0 g/dL	Based on CDC Data No race adjustment
World Health Organization (2011)	Hb < 11.0 g/L	May fall 0.5 g/dL in T2
British Committee for Standards in Hematology (2012)	T1: Hb < 11.0 g/dL T2: Hb < 10.5 g/dL T3: Hb < 11.0 g/dL	

Where do Hb Thresholds Come From?

TABLE 2. Pregnancy month-specific and trimester-specific hemoglobin (Hb) cutoffs*

Gestation (wks)	12	16	20	24	28	32	36	40
Trimester	1[†]	2	2[†]	2	3	3[†]	3	term
Mean Hb (g/dL)	12.2	11.8	11.6	11.6	11.8	12.1	12.5	12.9
5th percentile Hb values (g/dL)	11.0	10.6	10.5	10.5	10.7	11.0	11.4	11.9
Equivalent 5th percentile Hct [§] values (%)	33.0	32.0	32.0	32.0	32.0	33.0	34.0	36.0

*Based on pooled data from four European surveys of healthy women taking iron supplements (7–10).

[†]Hb values adopted for the trimester-specific cutoffs.

[§]Hematocrit.

Centers for Disease Control: **CDC criteria for anemia in children and childbearing-aged women.** *Morb Mortal Wkly Rep* 1989, **38**:400-404; Centers for Disease Control: **Recommendations to Prevent and Control Iron Deficiency in the United States.** *Morb Mortal Wkly Rep* 1988; 47(RR-03):1-29

Source of Hb Threshold Data

- Thresholds established in relatively small study populations
 - <400 women in total from all 4 pooled studies
- Racial composition was not mentioned (Finland, UK, Sweden)
 - Minority composition of these populations was likely not representative of current North American population
- The ppBMI was specified in only 2 studies (~18-21 kg/m²)
 - ppBMI not representative of current North American population
- Supplemental Fe given across gestation ranged from 65-200 mg/d
 - >7 times higher than RDA of 27 mg of Fe per day

Applicability of Hb Thresholds - Concerns

- Often assume ~50% of anemia is caused by iron deficiency (ID)
- Many published studies do not report data on ID, anemia and iron deficiency anemia (IDA)
- When these data are reported, only a small percentage of the reported anemia prevalence can be classified as IDA
- This may be a consequence of:
 - Inaccurate Hb cut-offs (incorrect anemia prevalence)
 - Inaccurate cut-offs for iron status biomarkers (need to account for stage of gestation, plasma volume expansion, or inflammation)
 - Other nutrient deficiencies contributing to the observed anemia in relatively well-nourished North American pregnant populations

Pregnant Groups at Increased Risk for ID?

- NHANES data (Gupta et al., AJCN 2017)
 - Late trimester, women with parity ≥ 2
 - Non-Hispanic Black > Hispanic > Non-Hispanic White
- Women carrying multiple fetuses (Ru, AJCN 2016)
 - ID (SF < 12 ug/L) in 37% of women at 24 weeks
 - Anemia found in 34% at delivery (35 wks); **3-fold increase**
- Pregnant adolescents (Lee, J Nutr 2014)
 - ID (SF < 12 ug/L) in 22% of teens at mid-gestation (24 weeks)
 - Anemia found in 35% of teens at delivery; **3-fold increase**
- Women with pre-existing inflammation? Obesity?

HEIRS Study - Race/Ethnicity and Fe

Table 2. Prevalence of Elevated Iron Levels According to Race or Ethnic Group.*

Iron Test	No. of Participants (N=98,529)	Native American (N=645)	Asian (N=12,672)	Black (N=26,847)	Hispanic (N=12,337)	Multiple (N=1444)	Pacific Islander (N=689)	Unknown (N=442)	White (N=43,453)
						percent ±SE			
Ferritin levels >400 µg/ liter (men) or >300 µg/liter (women)	8652	6.36±0.96	19.00±0.35	9.67±0.18	5.26±0.20	12.53±0.87	25.40±1.66	7.69±1.27	5.91±0.11
Ferritin levels >500 µg/ liter (men) or >400 µg/liter (women)	4816	3.26±0.70	11.26±0.28	5.37±0.14	2.69±0.15	7.76±0.70	16.69±1.42	4.52±0.99	3.10±0.08
Ferritin levels >600 µg/ liter (men) or >500 µg/liter (women)	2777	1.71±0.51	6.54±0.22	3.27±0.11	1.46±0.11	4.78±0.56	11.76±1.23	2.71±0.77	1.65±0.06
Ferritin levels >1000 µg/ liter	364	0.62±0.31	0.58±0.07	0.53±0.04	0.28±0.05	0.69±0.22	1.31±0.43	0.45±0.32	0.20±0.02
Transferrin saturation >45%	7763	6.67±0.98	13.97±0.31	4.52±0.13	5.93±0.21	6.72±0.66	6.68±0.95	7.24±1.23	8.81±0.14
Transferrin saturation >50%	4322	3.72±0.75	7.68±0.24	2.55±0.10	3.37±0.16	3.60±0.49	3.05±0.65	4.30±0.96	4.91±0.10
Transferrin saturation >60%	1497	1.71±0.51	2.33±0.13	1.06±0.06	0.92±0.09	1.52±0.32	1.31±0.43	1.13±0.50	1.74±0.06
Ferritin levels >400 µg/ liter (men) or >300 µg/liter (women), and transferrin satu- ration >45%	1732	0.93±0.38	4.43±0.18	1.34±0.07	1.08±0.09	2.08±0.38	2.90±0.64	1.13±0.50	1.42±0.06
Ferritin levels >500 µg/ liter (men) or >400 µg/liter (women), and transferrin satu- ration >45%	812	0.47±0.27	1.87±0.12	0.75±0.05	0.47±0.06	0.90±0.25	1.02±0.38	0.23±0.23	0.67±0.04
Ferritin levels >400 µg/ liter (men) or >300 µg/liter (women), and transferrin satu- ration >50%	356	0.31±0.22	0.59±0.07	0.39±0.04	0.21±0.04	0.48±0.18	0.44±0.25	0.23±0.23	0.31±0.03
Ferritin levels >300 µg/ liter (men) or >200 µg/liter (women), and transferrin satu- ration >50% (men) or >45% (women)	1958	1.24±0.44	4.84±0.19	1.44±0.07	1.34±0.10	1.87±0.36	3.05±0.65	1.36±0.55	1.68±0.06

- Hemochromatosis and Iron Overload Screening Study
- Serum ferritin highest among Pacific Islanders and Asians
- Transferrin saturation is highest among Asians
- Elevations in both serum ferritin and transferrin saturation were most prevalent in Asians
- Subpopulations of Asians may be at higher risk of excess body Fe stores

Ethnicity and Iron Status in Pregnancy?

- Possible impact of ethnicity on Fe status in pregnant and lactating women was examined in the HEIRS study (Gordeuk et al., AJCN 2017)
- Among women (25-44 y of age); n=20,080 women were nonpregnant or non-breastfeeding and n=1962 were pregnant or breastfeeding
- **Increased** risk of ID was found among non-pregnant and non-breastfeeding Hispanic (OR:1.8; $p<0.001$) and African American women (OR:1.6; $p<0.001$)
- Asian-American ethnicity was associated with a **decreased** risk ($p=0.049$) of ID in both groups of women (non-pregnant/non-breastfeeding and in those pregnant or breastfeeding)
- Asian American ethnicity was associated with **significantly increased Fe stores** in non-pregnant, non-breastfeeding women (OR:1.8; $p=0.001$)

Summary - Iron

1. The evidence supports the benefits of maternal Fe supplementation with respect to its ability to improve maternal and neonatal hematological status. Other risk and benefits require further study.
2. Additional research is needed to determine optimal Fe supplementation doses and their impact on both **maternal and neonatal** hematological status.
3. More research is needed to evaluate the current Hb thresholds and cut-offs for Fe status biomarkers used to define anemia, ID and IDA during pregnancy
4. Race and ethnic differences in the risk of both ID and iron excess have been reported and merit additional research and attention

2011 DRI for Vitamin D During Pregnancy / Lactation



	Female		Pregnancy			Lactation		
	Age	EAR	EAR	RDA	UL	EAR	RDA	UL
D 2011	14-18 y	400	400	600	4000	400	600	4000
	19-50 y	400	400	600	4000	400	600	4000

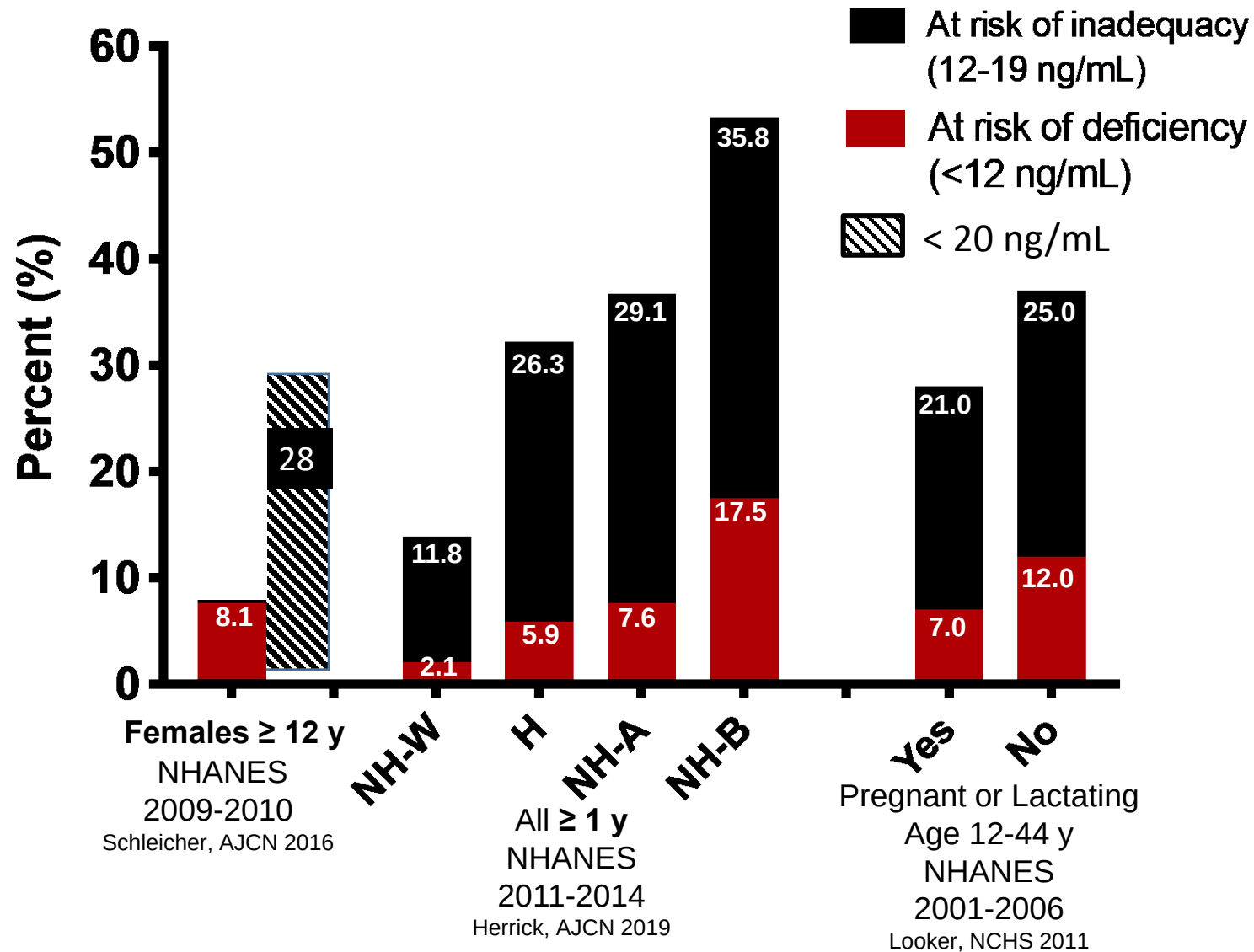
IOM recommends no increase during pregnancy

- No association between 25(OH)D and bone mass in pregnancy
- Animal studies do not “elucidate a specific function in fetal development”

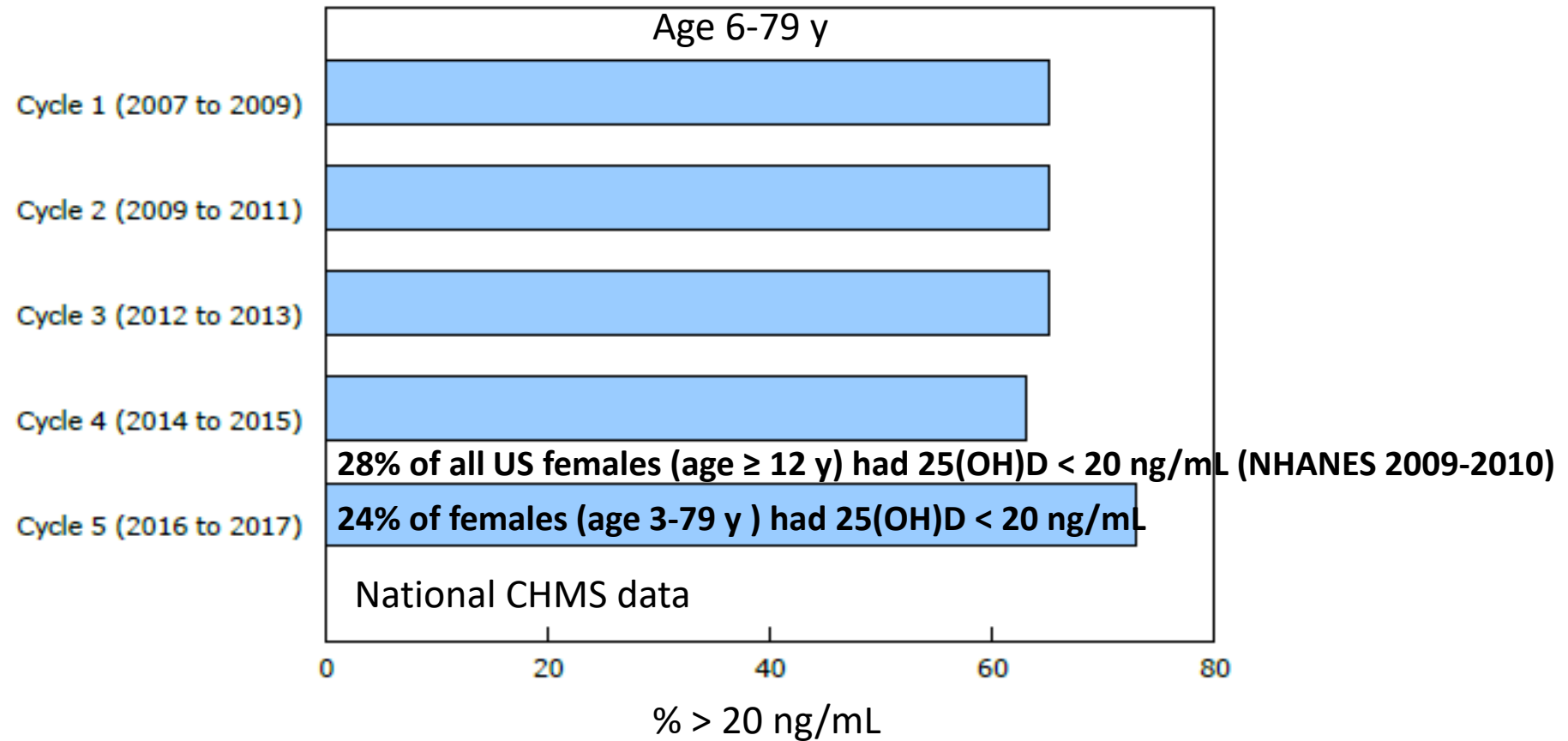
IOM recommends no increase during lactation

- No association between maternal 25(OH)D and BMD or milk [Ca]
- Breast milk [D] “remains unchanged with supplementation at least up to 2,000 IU/d”

Vitamin D Status of the U.S. Population



Vitamin D Status of Canadian Population



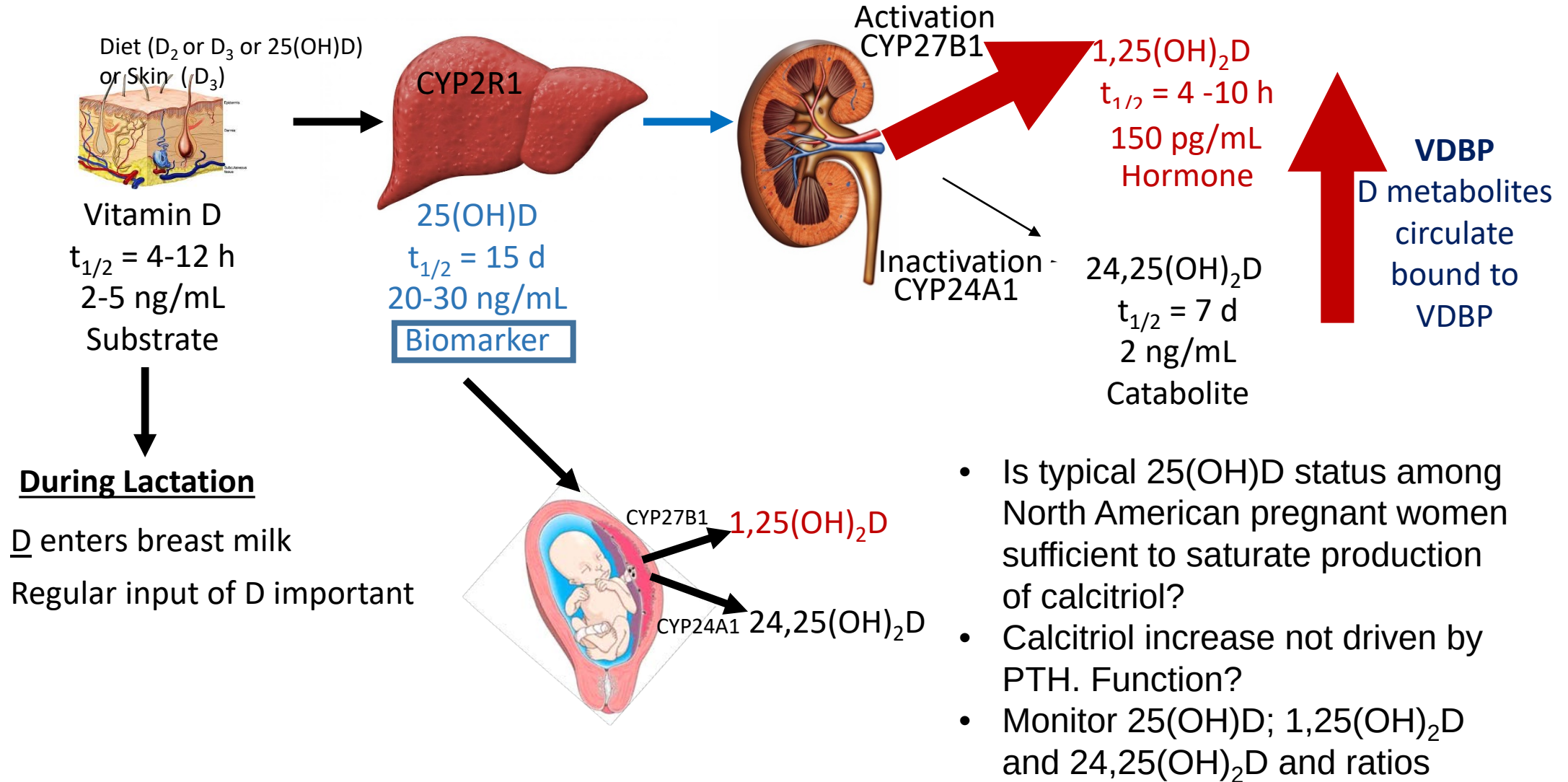
<https://www150.statcan.gc.ca/n1/daily-quotidien/190206/dq190206c-eng.htm>

How Much D, What is the Evidence, Outcome, and Best Biomarker?



Heyden et al., J Steroid Biochem 2018; 180:41-50

Vitamin D Biomarkers During Pregnancy?



D Supplementation in Pregnancy

Cochrane and systematic reviews of maternal D supplementation have found maternal D supplementation to increase maternal 25(OH)D status and neonatal cord D concentrations but findings on the impact of D supplementation on maternal and neonatal birth outcomes are not consistent.

- Variable study designs: [D, D+Ca, D+Ca+MVM, D+MVM] vs [no treatment, placebo, Ca, MVM]
- Variable dosing regimens: daily, weekly, bolus
- Total D dose across gestation varies: <56,000 - >200,000 IU
- Stage of gestation when supplementation initiated varies
- Pre-pregnancy BMI often not reported
- Analytical approaches for vitamin D measures vary

Summary – Vitamin D

1. More than 20% of North American females have 25(OH)D concentrations < 20 ng/mL
2. Vitamin D homeostasis over gestation is unique to any other life stage. Further work is needed to identify the effects of vitamin D metabolites at the systemic and cellular level during pregnancy to help inform vitamin D intake recommendations.

2011 DRI for Ca During Pregnancy / Lactation



		Non-Pregnant		Pregnancy		Lactation		
	Age	EAR	EAR	RDA	UL	EAR	RDA	UL
Ca 2011	14-18 y	1100	1100	1300	3000	1000	1300	3000
	19-50 y	800	800	1000	2500	800	1000	2500

IOM recommends no increase during pregnancy

- Increase in Ca absorption meets fetal demands
- No evidence of lower BMD after multiple pregnancies

IOM recommends no increase during lactation

- No evidence of lower BMD after extended breastfeeding
- Bone lost during lactation is recovered

Ca Supplementation in Pregnancy

Cochrane review of maternal Ca supplementation (vs. placebo or no treatment) found no clear benefits of Ca for the prevention of PTB or LBW. Bone health was a secondary outcome with few data evaluating maternal or neonatal BMD (Buppasiri et al; 2015, 2011)

- Form of Ca used varied: carbonate, gluconate, lactate, combined, not specified
- Timing of dosing regimen varied ≥ 20 wks (11 trials) or < 20 wks (n=5)
- Supplemental Ca (300 -2000 mg/d) and habitual Ca intake were highly variable
- Maternal BMD tested in only 1 study (1978 using radiographs)
- Neonatal BMD; 2 studies

Groups at Increased Risk?

- Pregnancy / lactation at extremes of maternal age?
- Women carrying multiple fetuses?
- Individuals ingesting very low calcium diets?

Summary - Calcium

1. The existing RCT evidence on the impact of calcium supplementation on maternal bone mass across pregnancy is limited.
2. Certain groups are likely at increased risk of Ca insufficiency across pregnancy but data in these populations are limited primarily to epidemiological studies, small longitudinal cohort studies or are extrapolated from animal studies.
3. What do we know now that we didn't know 30 years ago?.....

Future Studies – Fe-D-Ca

- Additional techniques are now available to visualize fetal bone development and maternal bone quantity and quality across gestation.
- Maternal, fetal and placental responses to nutrient exposures can be monitored using new approaches.
- Application of “omic” or multiomic technologies in pregnant and lactating women may help identify responses to nutrient status and supplementation or identify new processes that are impacted by nutrient exposures.

