Caffeine in Pregnancy and Lactation: What's New?

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Objectives

Describe preconception risks associated with caffeine consumption

Discuss prenatal effects and risk associated with caffeine intake, by trimester

Relate energy drinks and evidence for influence of caffeine / high sugar intake

Discuss differences in pregnancy risk based on polymorphisms in caffeine metabolism (slow or fast).

Caffeine Background

Most widely consumed psychostimulant worldwide, naturally found in coffee, tea, cocoa, chocolate[1]

Generally Recognized as Safe (GRAS) for consumers up to 400 mg/daily[2]

- 200 mg/day for pregnant women
- 300 mg/day for breastfeeding women (lower intake for pre-term, newborns)

FDA: list on ingredients panel if added to food, beverages; amount not required[1]

In the USA, two large national representative surveys monitor caffeine intake from food and beverages:

- The Kantar Worldpanel (KWP)[7]
- National Health and Nutrition Examination Survey (NHANES)[8]

Data is inconsistent; considerable controversy regarding caffeine safety and consumption during pregnancy[3-6; 11]

Image from US-FDA (2018 Dec. 18)

Caffeine Background

Additive in some medications, dietary supplements, cosmetics, foods:

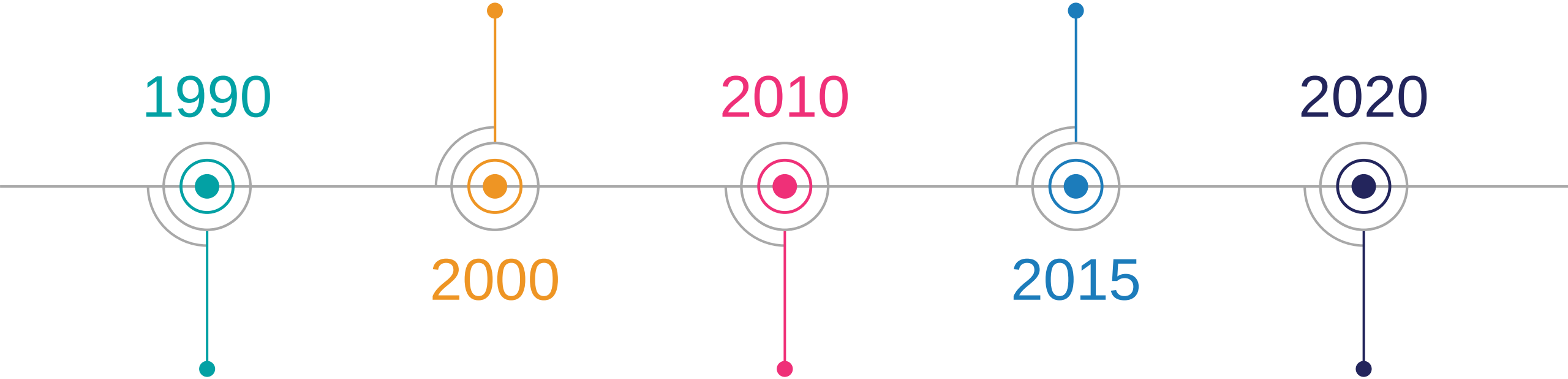
- Many dietary supplements haven't been tested in pregnant women, nursing mothers, or children[9]
- Often added to weight-loss dietary supplements, caffeine is found naturally in tea, guarana, kola nut, yerba mate, and other herbs[10, 44]

In past 20 years, caffeinated energy drinks, sports drinks, juices, water introduced; increasing in popularity.

- Energy drinks typically contain combinations of ingredients that may cause a more powerful stimulant effect
  - Guarana contains caffeine
- A 16-ounce energy drink contains up to 62 grams added sugar, exceeding amount recommended for an entire day[10]

Relate energy drinks and evidence for influence of caffeine / high sugar intake

Caffeine: Timeline of Related Events



- Safety in pregnancy: inconsistent data[3-6; 11]
- 1994 Dietary Supplement Health Education Act[13]
- Human Genome Project begins[12]

- Proliferation of new products (energy drinks)[14]
- Dietary Supplement Nonprescription Drug Consumer Protection Act[15]
- Facebook founded 2004[29]

- Energy drink controversy; regulatory scrutiny[25]
- 2014 Caffeine in Food/DS: Safety Workshop[11]
- CFSAN Adverse Events Reporting System[26]

- Internet sales of pure caffeine; FDA warning[16-17]
- Genome: New insights to caffeine metabolism[18-24]

FDA Pregnant women: clinical trials[27]
DSHEA 25-year anniversary
FDA Nutrition Facts label changes[28]

Dietary Supplement Health & Education Act (1994)[15]

Dietary Supplements are not regulated by the FDA the same way as medications[1]

Industry has grown from $4 billion to $40 billion in 25 years since DSHEA was passed[1; 30]

More than 90,000 supplements sold; some contain caffeine[1]

Manufacturers are responsible for ensuring product safety and correct labeling[1; 15]

FDA is proposing new efforts to strengthen regulation of dietary supplements by modernizing and reforming oversight[16; 30]

Supplement vs. Nutrition Labels

DIETARY SUPPLEMENTS FALL UNDER REGULATORY GUIDELINES OF THE 1994 DIETARY SUPPLEMENT HEALTH & EDUCATION ACT[15]

FOODS & SOME BEVERAGES FALL UNDER REGULATORY GUIDELINES OF **THE FOOD, DRUG, AND COSMETIC ACT** [15]

Supplement Facts
Serving Size: 1 Can (12 fl. oz.)

Amount Per Serving		% Daily Value**
Calories	45	
Total Carbohydrate	11g	4%
Sugars	9g	
Vitamin C	50mg	83%
Vitamin D	200IU	50%
Vitamin E	40IU	133%
Thiamin	1.5mg	100%
Riboflavin	2mg	100%
Niacin	20mg	100%
Vitamin B6	2mg	200%
Vitamin B12	12mcg	200%
Biotin	150mcg	50%
Pantothenic Acid	10mg	100%

Amount Per Serving		% Daily Value**
Calcium	31mg	3%
Magnesium	40mg	10%
Potassium	60mg	2%

Proprietary Blend 892mg †
Green Tea Extract, DL-Methionine, L-Glutamine, L-Arginine, D-Glucosamine, Quercetin,Co-Q10, Bilberry Extract,Turmeric Root,Omega-3 EFAs

**Percent Daily Value (DV) are based on a 2,000 Calorie diet. Your Daily Values may be higher or lower depending on your calorie needs

†Daily Value not established

Ingredients: Carbonated filtered water, blue agave nectar, natural flavors, citric acid, malic acid, gum acacia, stevia, green tea extract, DL-Methionine, L-Glutamine, L-Arginine Monohydrochloride, D-Glucosamine HCl, Monopotassium, Quercetin Dihydrate, Ascorbic Acid, Magnesium Lactate Dihydrate, Calcium Lactate Gluconate, Bilberry Extract, Ubidecarenone, Niacinamide,Turmeric Root,Omega-3 DHA/EPA, D-Calcium Pantothenate, Pyridoxine HCl, Riboflavin, Thiamin Mononitrate, Folic Acid, Biotin, Vitamin B-12, Vitamin D-3, DL-Alpha Tocopheryl Acetate, Vitamin A Palmitate

Allergen Statement: Contains Omega-3s derived from fish, soy and milk. Not recommended for children or women while nursing or pregnant. Keep out of reach of children. Consult your physician before starting any supplement regimen

Nutrition Facts
Serving Size 8.0 fl. oz. (240mL)
Servings Per Container 2

Amount Per Serving	Per 8 fl. oz.	%DV*	Per Can	%DV*
Calories	110		210	
Total Fat	0g	**0%**	0g	**0%**
Sodium	180mg	**8%**	370mg	**15%**
Total Carb	27g	**9%**	54g	**18%**
Sugars	27g		54g	
Protein	0g		0g	
Riboflavin (Vit. B2)		100%		200%
Niacin (Vit. B3)		100%		200%
Vitamin B6		100%		200%
Vitamin B12		100%		200%

Not a significant source of calories from fat, saturated fat, trans fat, cholesterol, dietary fiber, vitamin A, vitamin C, calcium and iron.

*Percent Daily Values are based on a 2,000 calorie diet.

INGREDIENTS: CARBONATED WATER, SUGAR, GLUCOSE, CITRIC ACID,

To purchase with Electronic Benefits Transfer card, energy drinks must bear a nutrition label [15; 28; 31]

Labeling Single-Serving Packages

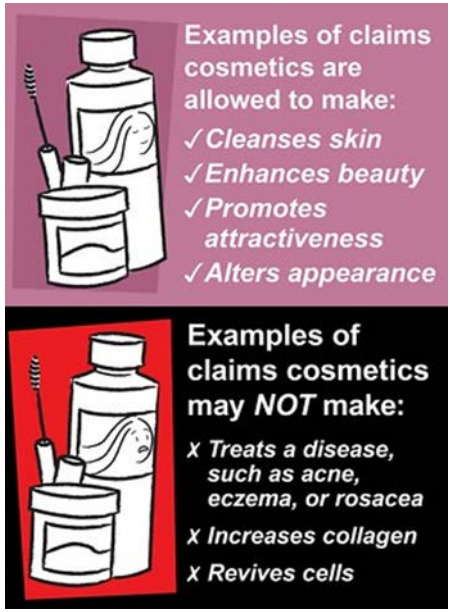
For packages between one and two servings, calories and other nutrients must be declared for the entire package rather than per serving because people typically consume the package in one sitting.

31. Mayne, S. (2018) *The new nutrition facts label.* Retrieved from: https://www.fda.gov/media/97724/download




Caffeine-Added Products Proliferating

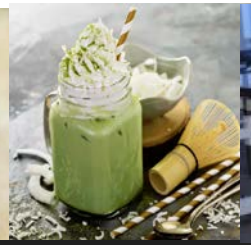
- Patterns of use, products are changing and not well understood[25]
- Readily available; attractive to many[25]
- Adverse Event Reports associated with foods, cosmetics, dietary supplements tracked in CAERS database[26]










FDA Warns Consumers About Pure and Highly Concentrated Caffeine[16]

Synthetic and pure powdered caffeine can be purchased on the Internet

One teaspoon of pure caffeine contains 5,000 milligrams (~28 cups of coffee)

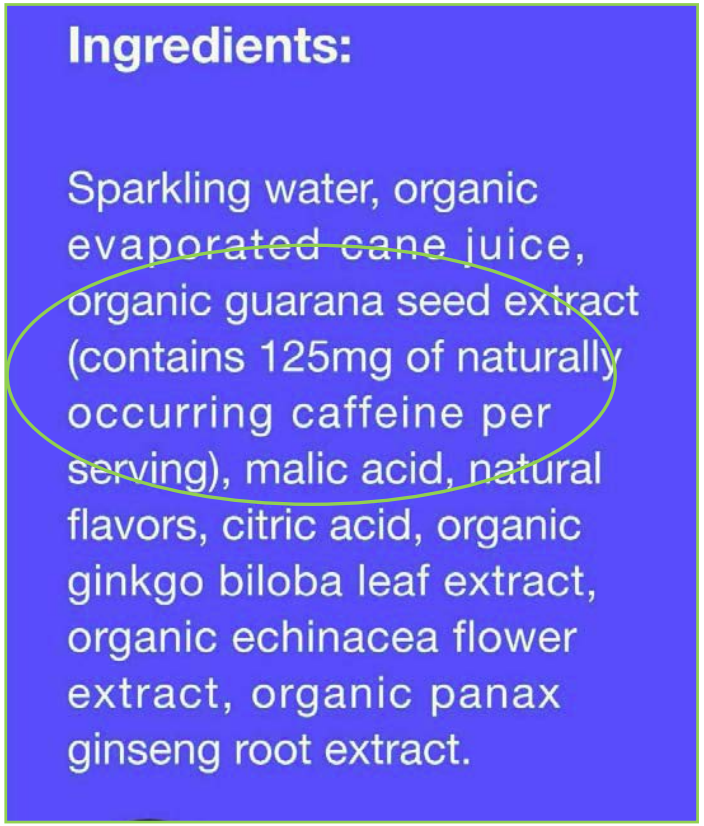
Difficult to gauge safe amount

FDA asking companies to take pure caffeine off the market for safety reasons

WARNING! Pure CAFFEINE Can be *HIGHLY TOXIC* if not used correctly. By Purchasing you agree, and are indicating that you are over 18 years of age, and that you are using for cosmetic purposes

Estimating Caffeine Exposure is Difficult for Foods & Supplements[1]

- The **amount** of caffeine as part of a "blend" does not need to be declared[1]
- Little known re: accuracy of reporting for energy products, consumption patterns[1]
- Difficult to estimate who is using, how often, and how much; reporting biases[32-33]
- Some supplements interact with a variety of lab tests, altering results[1]



Relate energy drinks and evidence for influence of caffeine / high sugar intake

1. Collect DNA sample
2. Mail to lab with payment
3. Learn if you are a “fast” or “slow” caffeine metabolizer

Image from: http://www.consumergenetics.com/DNA-Tests/Caffeine-Metabolism-Test.php

Caffeine Metabolism & Pharmacokinetics[3; 21, 23; 32; 4-35]

Metabolism, clearance, and pharmacokinetics is influenced by many factors

Genetic variability affects reaction to caffeine; may drive consumption

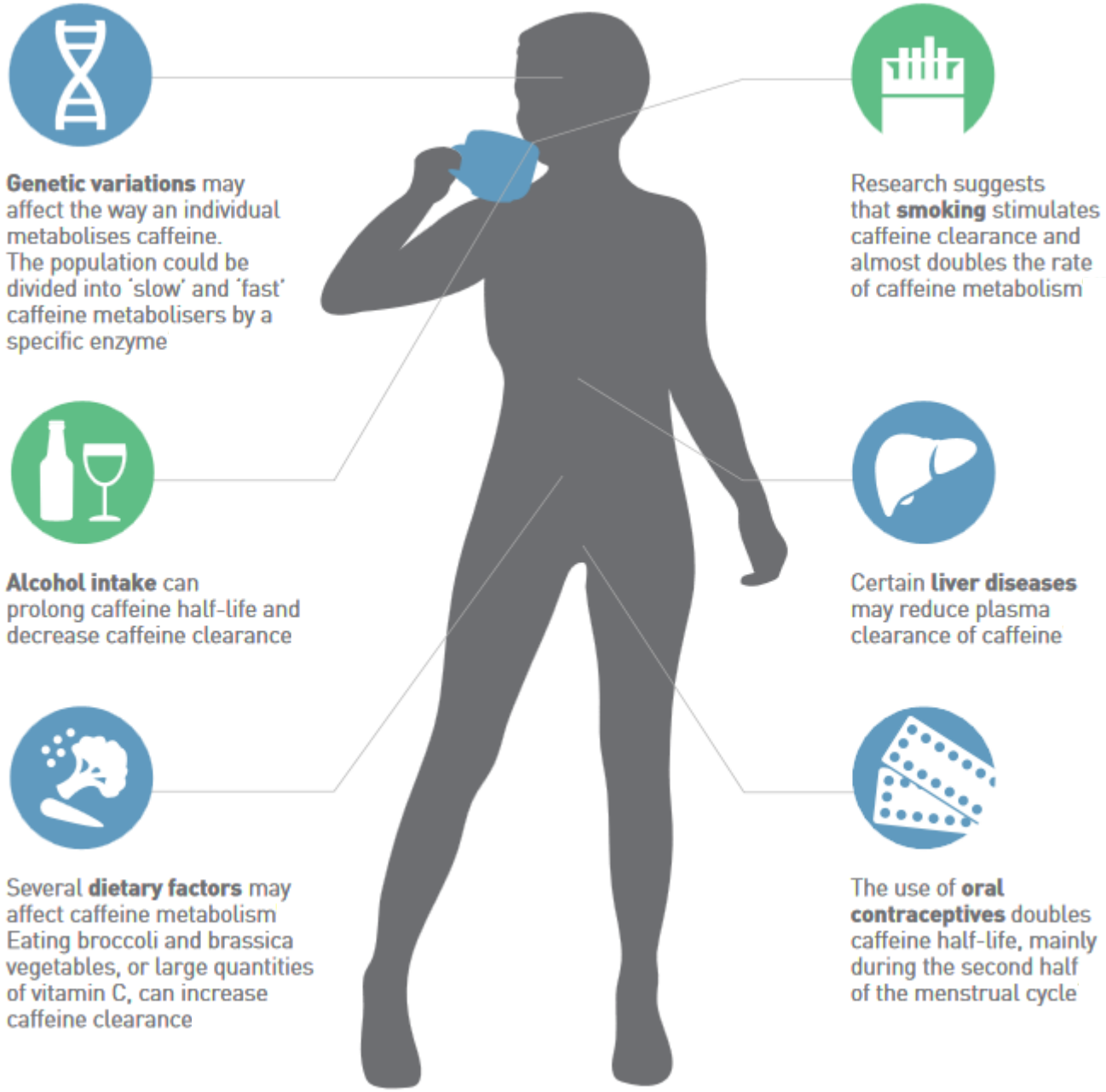
Genetic variability affects binding to brain receptors, influencing how we experience caffeine’ effect

- Caffeine has similar structure to adenosine; binds to receptors in brain
- Increases feeling of alertness
- Polymorphism of adenosine receptor ADORA2A found in caffeine-sensitive persons

Enzymes responsible for metabolizing caffeine: cytochrome P450

- CYP1A2 responsible for metabolizing 95% of ingested caffeine
- Genetic variation determine CYP1A2 activity in each person
- This polymorphism divides people into fast/slow metabolizers

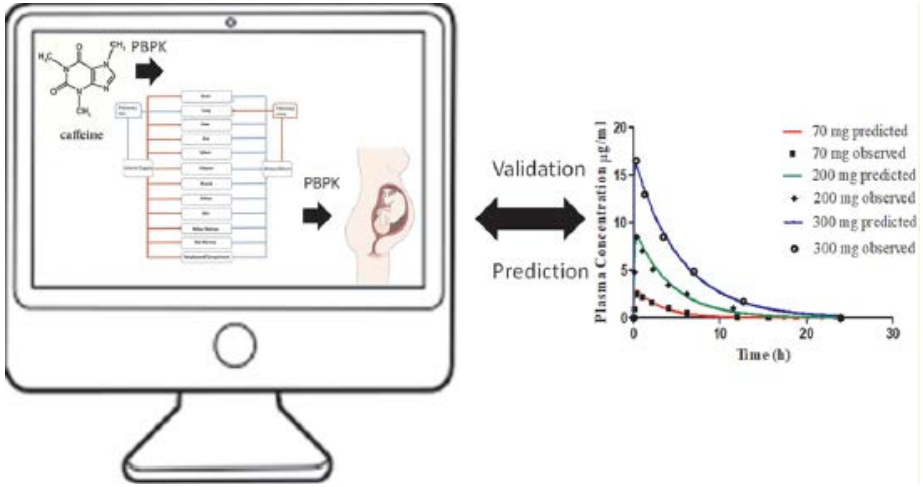
Factors affecting Caffeine Metabolism[18, 21, 23, 36]



Caffeine Metabolism [18-19 21, 23, 36-37]

- Variations of the gene affect how caffeine is metabolized, eliminated:
  - CYP1A2*1A allele: metabolizes caffeine rapidly
  - CYP1A2*1F allele: metabolizes caffeine slowly.
  - Risks:
    - >200 mg per day: may have increased risk of non-fatal myocardial infarction
    - 100-300 mg/day: increased risk of pregnancy loss, reduced fertility (Cornelius, 2016; Darakjian, 2019)
- Half-life depends upon:
  - Amount consumed
  - Liver function
  - Pregnancy (enzyme activity decreases by 50% 2nd and 3rd trimesters)
  - Concurrent medications may prolong half-life
    - Oral contraceptives, antibiotics, calcium antagonists, beta blockers, antidepressants, anti-psychotics, anti-inflammatory drugs, proton pump inhibitors, bronchodilators
  - Health status (obesity, smoking), age, gender

Caffeine Metabolism in…	Half-life
Healthy Adult	3-4 hours
Woman taking contraceptives	5-10 hours
Pregnant woman	9-11 hours
Liver disease	Up to 96 hours
Newborn	30 hours



The application of the physiological based pharmacokinetic/pharmacodynamic (PBPK/PD) model could provide a useful tool to help define potential cut-offs for caffeine intake in various stages of pregnancy [37]

Absorption [3; 35, 37]

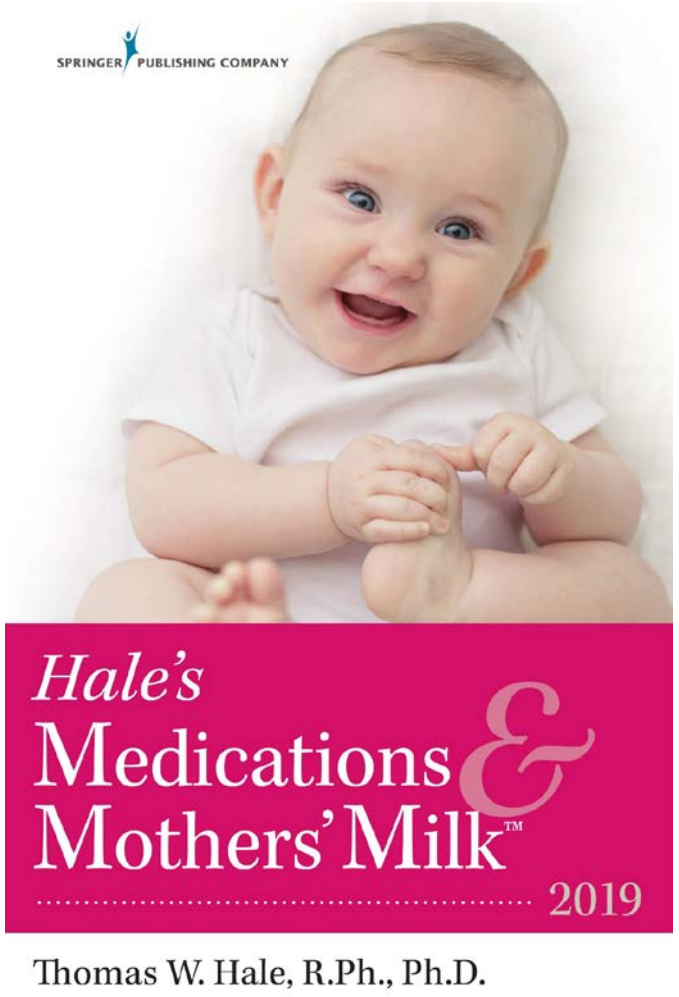
Caffeine & its metabolites readily cross placental barrier[37]
- Rely on maternal metabolism for caffeine clearance

Lactational pharmacology is complex: [3]
- *Which drugs are safe, and which are dangerous?*
- Most mothers could continue to breastfeed without risk to infant
- FDA now recommending drug manufacturers carry out studies

Drug enters milk, travels through baby's GI tract prior to absorption

Some drugs not stable in GI tract due to proteolytic enzymes, acids in infant's stomach

Absorption characteristics may decrease the effect of many drugs



Medications & Mother's Milk [3]

- Human milk best for infants, yet use of medications in breastfeeding mothers is controversial
- Most drugs don't enter milk in levels hazardous to baby Chronic coffee drinking may reduce iron content of breast milk (Nehlig, 1994)
- Occasional caffeine use not contraindicated, but persistent, chronic use may lead to high plasma levels in infant, particularly during neonatal period (Hale, 2019)
  - A Relative Infant Dose of <10% is considered safe; increasingly popular by investigators
  - Caffeine Relative Infant Dose (RID) range: 6-25.9%.
  - **Lactation Risk Category: L2:** Limited Data; Probably compatible FDA recognizes medications carry low risk to baby and recommend manufacturers carry out studies to determine milk levels of their drug

L1 Compatible
L2 Probably Compatible
L3 Probably Compatible
L4 Potentially Hazardous
L5 Hazardous

Interaction between maternal caffeine intake during pregnancy and CYP1A2 C164A polymorphism affects infant birth size in Hokkaido study (Sasaki et al., 2017)

- First study to consider effects of maternal caffeine intake during pregnancy and the CYP1A2 C164 polymorphism on infant birth size.
- Methods: Prospective cohort study Japan (n=476 mother-child pairs)
- Several CYP1A2 polymorphisms associated with in vivo changes
  - C164A polymorphism leads17 to a slow caffeine metabolizer phenotype (CC/CA) and a fast phenotype (AA) with higher ratios of caffeine metabolites
  - Maternal caffeine intake during pregnancy has impact on fetal development higher among women with fast caffeine metabolism than those with slow caffeine metabolism
- Conclusion: Non-smokers who rapidly metabolize caffeine may be at increase risk for having infants with decreased birth size when consuming >300 mg caffeine per day [35]

Safety of Ingested Caffeine: Comprehensive Review (Temple et al., 2017)

- Caffeine consumption is relatively safe
- Trend: alcohol mixed energy drinks may increase risk of harm
- For vulnerable populations (pregnant women, children, individuals with mental illness), consumption could be harmful [5]
- Recommend future research

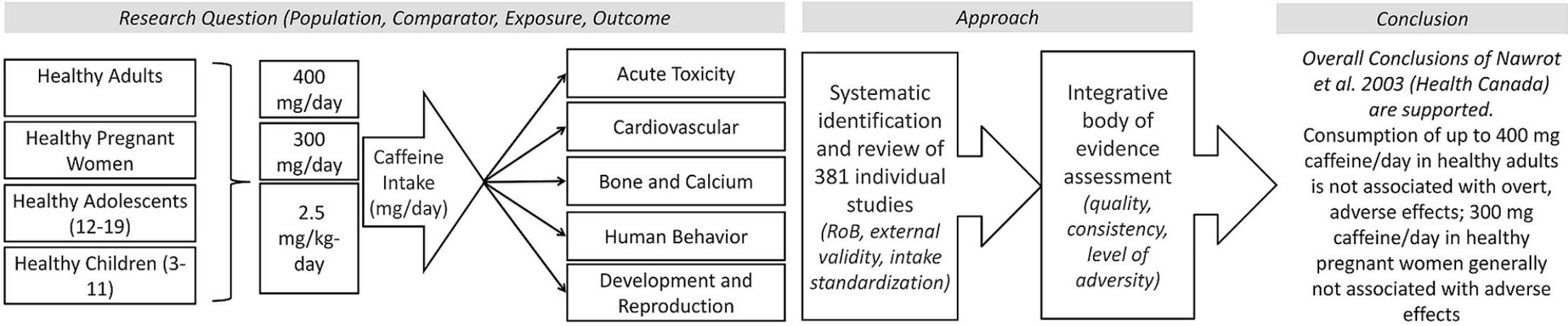
Effects of maternal caffeine consumption on the breastfed child: A systematic review (McCreedy et al., 2018)

Aim: To systematically review the evidence on the effects of maternal caffeine consumption during breastfeeding on the breastfed child.

Results: whether caffeine was the causal ingredient is questionable. The insufficient and inconsistent evidence available had quality issues impeding conclusions on the effects of maternal caffeine consumption on the breastfed child.

Conclusion: Evidence for recommendations on caffeine intake for breastfeeding women is scant, of limited quality and inconclusive.

Birth cohort studies investigating the potential positive and negative effects of various levels of maternal caffeine consumption on the breastfed child and breastfeeding mother could improve the knowledge base and allow evidence-based advice for breastfeeding mothers [4]



Systematic Review of Potential Adverse Effects of Caffeine Consumption in Healthy Adults, Pregnant Women, Adolescents, Children (Wikoff et al., 2017)

Over 10,000 peer-reviewed, caffeine safety papers have been published over past 20 years [6]

First review to apply systematic review methodologies to toxicological assessments [6]

Influence of Sugar, High Caffeine Intake: Results of 3 Studies [38-40]

- Caffeinated tea intake associated with slight reductions in fecundability in females; caffeinated soda and energy drink intake associated with reduced fecundability among males (n=2,135) (Wesselink et al, 2016)
- Daily caffeine consumption of >300 mg is associated (p <.03) with a 2-day increased gestational age at birth (van der Hoeven et al., 2017)
  - Healthy pregnancies (n=936) from WHISTLER birth cohort
  - Tea consumption significantly related to higher risk of pregnancy induced hypertension (p=0.004)
  - No associations concerning coffee consumption or birth weight/length observed
- Sugared beverages--independent of caffeine content--may be a bigger threat to reproductive success than caffeinated beverages without added sugar (Machtinger et al., 2017)
  - Aim: maternal intake of beverage type on IVF outcomes (n=340 women undergoing IVF)
  - Higher intake of sugared soda was associated with lower total, mature, & fertilized oocytes and top-quality embryos after ovarian stimulation
  - No associations found between consumption of coffee, caffeine, diet soda, and IVF outcome

Drugs & Lactation Database[2]

LactMed® is part of the National Library of Medicine's Toxicology Data Network (TOXNET®)

Search to learn about:

- How medication impacts breastfeeding mother and infant
- Medication levels in milk / blood of mother and infant.
- How a medication impacts the infant's health.
- Alternate medications to consider (when appropriate).

All data are derived from the scientific literature and are fully referenced.

Peer reviewers assure scientific validity and currency of data.

In 2020, over 45% of people worldwide own a smartphone and 50% use the Internet

mHealth Apps [41-43]

The unprecedented spread of mobile technologies to address health priorities has evolved into a field known as mHealth

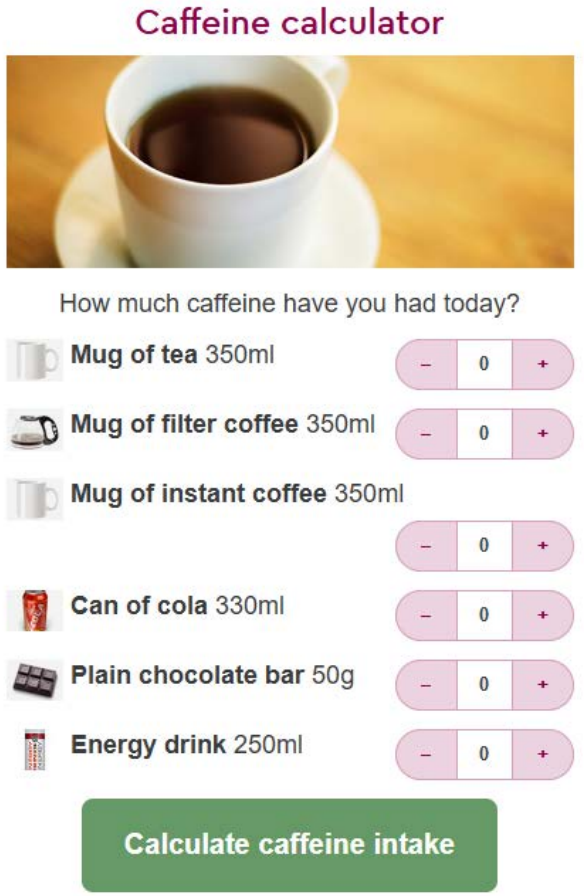
- Social media and mHealth apps are increasingly used in pregnancy care with emerging promising findings.
- In a meta-analysis (n=16), Chan & Chen (2019) found the interventions were useful with moderate to large effect sizes regarding maternal health, mental health, and knowledge about pregnancy [42]
  - weight management, gestational diabetes control, asthma control

Personal coaching apps guide healthy diet / lifestyle coaching based on self-test results

- May be used to facilitate pre-conception care in prospective parents

Use and rapid development of mHealth apps offers new opportunities to reach, educate large populations

mHealth usability model (Health-ITUEM) offers a framework for evaluating mobile health applications [43]



Take-Away Messages

- Pregnant, lactating women may turn to caffeinated beverages due to fatigue, sleep issues;[44] diffficult to measure consumption.
- Decreasing caffeine intake during pregnancy may represent a strategy to optimize fetal growth
- mHealth coaching apps offer promising methods for self-managing nutrition and lifestyle.
- Genome offering new insights to caffeine metabolism; FDA encouraging inclusion of pregnant women in clinical trials
- Worldwide, over45% own a smartphone; 50% use the Internet. Many women seek medical info here and on social media
- Most drugs don't enter breastmilk in levels hazardous to the baby; Relative Infant Dosing: <10% is relatively safe
- Energy drinks/shots contain large amounts of caffeine and assorted other ingredients that have not been fully studied

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Take-Away Messages

Caffeine metabolism slowed in pregnancy; Lactmed®: 200mg/day pregnant; 300 mg breastfeeding

Encourage patients to read ingredient labels for sugar and caffeine

Resources to inform, facilitate research on this topic:

- Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS)
- Dietary Supplement Label Database
- Dietary Supplement Ingredient Database
- LactMed® Drug & Lactation Database
- National Health and Nutrition Examination Survey (NHANES)
- Kantar Worldpanel Online Data Delivery and Analysis Tool

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