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Prenatal Supplement Formulations

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Objectives

- Discuss variations in routine prenatal multivitamin and mineral (PMVM) formulations
- Describe bioavailability of PMVM formulations
- Identify characteristics of PMVMs that indicate high quality
  - Quality assurance
  - Potential patient safety issues
- Review differences in sources of nutrient supplements for PMVMs

Introduction: PMVM Labels

Supplement Facts

Each Tablet Contains:	Amount per Tablet	% Daily Value
Vitamin A (Acetate and Beta Carotene)	4000 I.U.	80%
Vitamin C (Ascorbic acid)	120 mg	200%
Vitamin D-3 (Cholecalciferol)	400 I.U.	100%
Vitamin E (dl-Alpha Tocopheryl Acetate)	22 mg	73%
Vitamin B-1 (Thiamine Mononitrate)	1.84mg	123%
Vitamin B-2 (Riboflavin)	3 mg	176%
Niacin (Niacinamide)	20 mg	100%
Vitamin B-6 (Pyridoxine HCl)	10 mg	500%
Folic Acid	1 mg	200%
Vitamin B-12 (Cyanocobalamin)	12 mcg	200%
Calcium (from Calcium Carbonate)	200 mg	20%
Iron (Ferrous Fumarate)	27 mg	150%
Zinc (Zinc Oxide)	25 mg	167%
Copper (Cupric Oxide)	2 mg	100%

Multivitamin/Multimineral Tablet

Supplement Facts

Serving Size: 1 Tablet
Servings Per Container: 30

	Amount Per Serving	% DV for Pregnant and Lactating Women
Vitamin A (as Beta-Carotene)	900 mcg RAE (3000 IU)	69%
Vitamin C (Ascorbic Acid)	120 mg	100%
Vitamin D (as Cholecalciferol)	10 mcg (400 IU)	67%
(as dl-Alpha Tocopheryl Acetate)		
Thiamin (as Thiamine Mononitrate)	1.8 mg	129%
Riboflavin	4 mg	250%
Niacin (as Niacinamide)	20 mg NE	111%
Vitamin B_6	25 mg	1250%
Folate	1667 mcg DFE (1000 mcg Folic Acid)	278%
Calcium (as Calcium Carbonate)	200 mg	15%
(from Ferrous Bisglycinate and Iron Protein Succinylate)		
(as Magnesium Oxide)		
Zinc (as Zinc Oxide)	25 mg	192%
Copper (as Cupric Oxide)	2 mg	154%

*30 mg dl-Alpha Tocopheryl Acetate equivalent to 15 mg Alpha-Tocopherol

Omega-3 Fatty Acid Capsule

Supplement Facts

Serving Size: 1 Softgel Capsule
Servings Per Container: 30

	Amount Per Serving	% DV for Pregnant and Lactating Women
DHA (Docosahexaenoic Acid)	200 mg	†

† Daily Value (DV) not established

Photo: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=161f0d6c-a272-42d9-bd04-576e6065b234&type=display
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PMVM Labeling Information

Evaluation of two public databases with label information for PMVM products

Characteristic	Nonprescription PMVM	Prescription PMVM
Number of products evaluated	82	132
Number of vitamins (mean±SE)	11±0.3	9±0.2
Number of minerals (mean±SE)	8±0.3	4±0.1
Folic acid content		Higher
Vitamin A content	Higher	
Vitamin D content	Higher	
Iodine content	Higher	
Calcium content	Higher	
% containing botanical ingredients	33%	9%
% containing probiotics	8%	2%

Saldanha L, et al. J Acad Nutr Diet. 2017 ;117(9): 1429–1436. doi:10.1016/j.jand.2017.04.002.

PMVM Labeling Information

Evaluation of actual prescription and nonprescription products

Ingredient	RDA or AI	Nonprescription PMVM (n=163) Mean (±SD)	Prescription PMVM (n=88) Mean (±SD)	Comparison of reported amounts	% Nonprescription PMVM correct RDA deficit	% Prescription PMVM correct RDA deficit
Calcium	1000 mg	**246.5 (±262.5)**	118.4 (±92.2)	p< 0.0001	73%	60.2%
Iodine	220 mcg	**95.4 (±90.3)**	53.5 (±78.1)	p=0.0003	NA	NA
Vitamin D	600 IU	**637.1 (±580.8)**	432.6 (±259.9)	p=0.0002	32.5%	25%
Iron	27 mg	22.9 (±10.2)	**33.1 (±20.1)**	p<0.0001	87.1%	95.5%
Folic acid	600 mcg	759.7 (±191.5)	**982.1 (±151.8)**	p< 0.0001	96.3%	98.9%
Choline	450 mg	**21.0 (±62.7)**	3.3 (±13.7)	P<0.0007	2.5%	0%

DeSalvo K, Stamm CA, Borgelt LM. J Am Pharm Assoc. 2018;58:258-67.

Variations in PMVM Labeling: Incorrect Labeling

- Relationship between labeled and analytically measured contents
- 24 prescription products evaluated from retail and mail-order pharmacies

LABELS

- All listed: folic acid, vitamins B-6, D, E and iron
- 83-92%: niacin, riboflavin, thiamin, and vitamins C, B12, and zinc
- 71%: calcium
- 46-54%: vitamin A, iodine, and DHA

CONTENT

- Overages of ≥ 20%: folic acid, niacin, riboflavin, vitamins A, B12, and D
- Overages of 10-15%: vitamins B6, C, and E
- Overages of 1-11%: docosahexaenoic acid (DHA)
- Below label results of 4%: thiamin

Andrews K, et al. Curr Dev Nutr. 2019;3(Suppl 1): nzz039.OR14-08-19.

Variations in PMVM Labeling: Incorrect Labeling

- Relationship between labeled and analytically measured contents
- 20 nonprescription and 16 prescription products evaluated
  - Key ingredients: folic acid, vitamin B6, vitamin C

LABELS

- When combined with average dietary intake 95% of nonprescription and 88% of prescription PMVMs met the daily recommended intake during pregnancy

CONTENT

- When combined with average dietary intake 79% of nonprescription and 82% of prescription PMVMs met the daily recommended intake during pregnancy

Jones J, Stamm CA, DeSalvo K, Borgelt LM. Manuscript in preparation.

Variations in PMVM Labeling: Unclear Labels

- Study evaluated synthetic folic acid content on PMVM labels
- Data from Dietary Supplements Label Database and DailyMed
- Results
  - Recommendations unclear re: dietary folate equivalents vs mcg folic acid
  - Amounts ≥ 800 mcg folic acid (prior daily value)
    - 99% of 79 prescription labels
    - 91% of 121 nonprescription labels
  - Labeled amounts higher than USPSTF recommended daily intake

Need consistent and clear recommendations for expression of folate and folic acid including labeling, daily value, upper limits, criteria for making health claims, and national recommendations.

Saldanha L, et al. Curr Dev Nutr. 2019 Jun; 3(Suppl 1): nzz048.P11-024-19.

Variations in PMVM Labeling: The Iron Debate

- Ferrous salts vary in PMVM formulations
  - 1 g of ferrous sulfate = 200 mg elemental iron (20% iron)
  - 1 g of ferrous fumarate = 330 mg elemental iron (33% iron)
  - 1 g of ferrous gluconate = 120 mg elemental iron (12% iron)
- Ferrous sulfate most commonly used in clinical trials, but was not present in 148 nonprescription and 101 prescription PMVMs (mostly ferrous fumarate)
  - Nonprescription PMVM range of elemental iron: 9-60 mg/serving
  - Prescription PMVM range of elemental iron: 4.5-106 mg/serving

Need additional research to evaluate chemical forms, bioavailability, and safety profiles, especially in iron-replete and iron-deficient pregnant women.

Saldanha L, et al. J Nutr. 2019;149:890-3.

Non-prescription PMVM Calculator

- Dietary Supplement Ingredient Database
- National estimates for 20 ingredients in non-prescription PMVMs
  - From multiple lots of 71 different non-prescription PMVMs
  - 10 vitamins and 10 minerals were analyzed
  - Reported predicted mean percent differences from label levels
  - Differences substantially higher for iodine, potassium, and chromium
  - Differences lower for thiamin, niacin, and vitamin B12
  - Regression equations predict mean differences from label levels
- Calculator available at: https://dietarysupplementdatabase.usda.nih.gov/prenatal_MVM.php

Andrews K, et al. Non-prescription Prenatal Multivitamin/mineral (MVM) Dietary Supplement Study. Available at: https://dietarysupplementdatabase.usda.nih.gov/dsid_database/Prenatal_MVM_%20res%20summary%207-31-17final.pdf

Summary: PMVM Formulations

- There is inconsistent information expressed on PMVM labeling
- There are differences between what is expressed on the label and actual content for some (but not all) PMVM ingredients
- There are some differences between nonprescription and prescription PMVM products, but this may not be clinically significant in a healthy population
  - This may have benefits for access and cost to patients
- Resources are available to determine estimated amounts of ingredients consumed in nonprescription products
  - Could there be a way to add dietary information to this?

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PMVM Characteristics and Bioavailability

- PMVM (and similar terms) have no standard or defined meaning
- PMVM products can have widely varied composition (e.g., ingredients, dose, salt forms) and evolve over time
- Patients and providers may interpret “PMVM” differently (e.g., DHA)
- Bioavailability typically described as absorption
  - Differs with each ingredient
  - Affected by host factors (e.g., homeostatic mechanisms)
    - Example: iron absorption or excretion dependent on iron status of person
  - Affected by size of ingested load
    - Example: absorption of calcium varies inversely as logarithm of load size
    - Example: single high doses of folic acid exceed metabolic capacity for reduction and methylation
  - Higher bioavailability is not necessarily better

Yetley E. Am J Clin Nutr. 2007;85(suppl):269S-76S.

PMVM Product Formulation Factors: Bioavailability

- Factors that affect product dissolution (release from dosage form)
  - Different chemical forms or nutrient interactions may affect bioavailability
    - Example: different forms of inorganic iron or zinc vary in bioavailability
    - Example: vitamin C interacting with inorganic iron may enhance iron bioavailability
    - Example: decreasing levels of magnesium or calcium increases iron bioavailability

Yetley E. Am J Clin Nutr. 2007;85(suppl):269S-76S..

PMVM Product Formulation Factors: Bioavailability

- Factors related to excipients or inactive ingredients that may affect drug stability, drug absorption, and metabolic processes
  - Affect completeness or rate of release for nutrients like calcium, vitamin E, pyridoxal phosphate, iron, folic acid, and vitamin B-12
  - Vitamin D intake can facilitate the absorption of essential inorganic elements (e.g., calcium, magnesium, copper, zinc, iron, and selenium) and the uptake of toxic elements (e.g., lead, arsenic, aluminum, cobalt, and strontium)

- Tested by dissolution (USP standard) - voluntary

Yetley E. Am J Clin Nutr. 2007;85(suppl):269S-76S. Schwalfenberg GK, Genius SJ. ScientificWorldJournal. 2015;2015:318595.

Ingredient Interactions of PMVMs

- Micromedex search “prenatal vitamins”: 171 drug-drug interactions
  - Contraindicated: 1
  - Major: 23
  - Moderate: 112
  - Minor: 35

Example Drug Interactions for PMVMs

Drug-Drug Interaction	Severity and Documentation	Summary
Simvastatin –Niacin	Major (Excellent)	Increased niacin and simvastatin exposure; increased risk of myopathy or rhabdomyolysis.
Iron-Ofloxacin	Moderate (Good)	Decreased ofloxacin effectiveness.
Iron-Zinc	Moderate (Excellent)	Decreased gastrointestinal absorption of iron and/or zinc.

Prenatal vitamins. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed January 16, 2020.

What Would You Choose?

OR

Photos: https://www.nia.nih.gov/health/dietary-supplements and https://www.hiv.gov/blog/when-undetectable-unachievable-study-offers-insights-hiv-persistence

Human Characteristics and Bioavailability of PMVMs

- Obesity
  - Associated with lower vitamin A, D, E, and K levels
    - Volumetric dilution and dysregulated hepatic signaling

Vanlint S. Nutrients. 2013;5(3):949-56. Traber M, et al. Am J Clin Nutr. 2017;105(3):571-9.
Trasino SE, et al. Sci Rep. 2015;5:15893. Shea MK, et al. J Nutr. 2010;140(5):1029-34.

Summary: Bioavailability

- Definitions and requirements regarding bioavailability are not established
- Many PMVM and human characteristics can affect bioavailability
- Drug interactions with PMVM ingredients rarely systematically evaluated, but could interfere or augment drug effects
- Individualized approach to PMVM supplementation may be ideal, but may not be feasible

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PMVM Quality Assurance

- USP verified mark (quality-supplements.org)
  - Contains ingredients listed on the label, with declared potency and amounts
  - Does not contain harmful levels of specified contaminants
  - Will break down and release into the body within a specified amount of time
  - Made according to FDA current Good Manufacturing Practices using sanitary and well-controlled procedures
- NSF content certified mark (nsf.org)
- Consumer Lab (ConsumerLab.com)
- Avoid products with health claims

https://www.usp.org/verification-services/verified-mark
https://www.nsf.org/newsroom/nsf-international-unveils-new-contents-certified-and-certified-for-sport-ce

Patient Safety: PMVM Additives

Heavy Metal Contamination

- 26 common PMVMs (Canada)
- 20/51 exceeded standards for lead toxicity (0.50 µgm/day)
- 3/51 exceeded acceptable arsenic levels
- Aluminum, nickel, titanium, and thallium detected in all samples
- 14/50 had detectable mercury but all within acceptable limits
- No correlation between cost and level of contamination

Recommendations

- PMVMs should be tested for toxic elements
- Guidelines for maximal acceptable levels, including cumulative exposure of toxic agents, should be established
- Emphasize preconception care to ensure use of high quality products
- Additional regulation of products (e.g., safety and purity through industry with government oversight and accountability)

Schwalfenburg G, et al. Toxicol Rep. 2018;5:390-5.

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Omega-3 supplements (fish oil) or primary sources (fish)?

- Omega-3s are essential for neurological and early visual development of the baby and have positive effects on pregnancy
- Three types of omega-3 fatty acids
  - Fish oils contain docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)
  - Plant sources with alpha-linolenic acid (ALA) - converted into omega-3 in body
- Best sources of DHA and EPA are cold-water fish or shellfish such as salmon, tuna, sardines, anchovies, and herring (2 servings per week)
  - Concerns about mercury and other toxins in fish, especially in pregnancy
- Purified fish oil supplements or fortified foods may be the safest source of EPA and DHA

https://americanpregnancy.org/pregnancy-health/omega-3-fish-oil/
https://www.acog.org/Patients/FAQs/Nutrition-During-Pregnancy?IsMobileSet=false

Folate or Folic Acid

- **Folate** (vitamin B9) occurs in several foods – liver, leafy vegetables, peas, beans, avocado, eggs, and milk
- **Folic acid** available in PMVMs, MVMs, pure supplements, and used to fortify foods (flour, pasta, breads, etc.)
- Folate and folic acid converted to metabolically active form: **L-5-methyltetrahydrofolate**
  - Calcium salt form of this available in some vitamin supplements
- Folic acid supplements, dietary folate, and L-5-methyl-THFL supplements have similar increases in plasma folate and red cell folate concentrations; some experts favor L-5-methyl-THFL due to potential genetic polymorphisms that impact conversion

Pietrzik K, et al. Clin Pharmacokinet. 2010;49(8):535. Greenberg JA, Bell SJ. Rev Obstet Gyneol 2011;4:126-7.
https://ods.od.nih.gov/factsheets/Folate-HealthProfessional

Conclusions

- There is great variation in PMVM formulations that calls for standardization on labels and in content
- Bioavailability of PMVM formulations varies based on characteristics of the PMVM as well as the person taking the PMVM
- High quality PMVMs can be readily accessed with the help of third-party testing, but additional regulation may be needed for safety
- While some differences exist for sources of nutrient supplements, they may not be relevant or significant with a healthy, adequate diet.