Fertility challenges: The impact of gut microflora and gut dysbiosis

2023 CDID Symposium
April 14, 2023

Jeffrey Moss, DDS, CNS, DACBN
jeffmoss@mossnutrition.com

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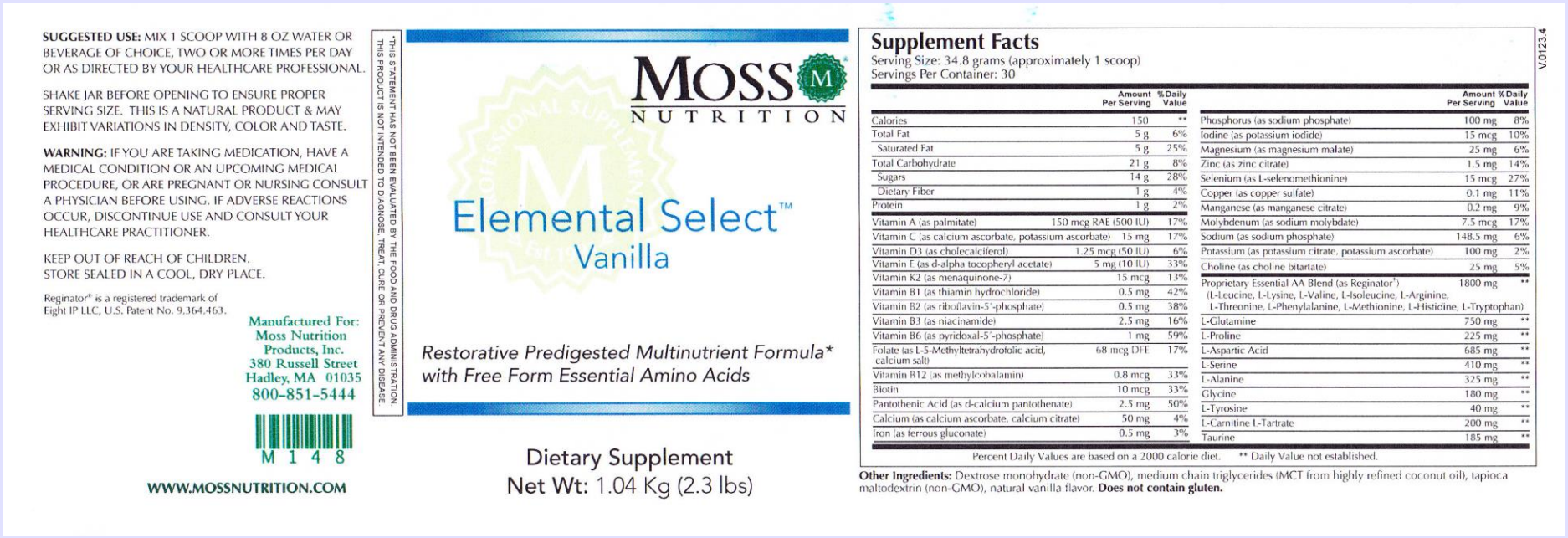

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Dietary Supplement
Net Wt: 1.04 Kg (2.3 lbs)

Supplement Facts

Serving Size: 34.8 grams (approximately 1 scoop)
Servings Per Container: 30

	Amount Per Serving	%Daily Value
Calories	150	**
Total Fat	5 g	6%
Saturated Fat	5 g	25%
Total Carbohydrate	21 g	8%
Sugars	14 g	28%
Dietary Fiber	1 g	4%
Protein	1 g	2%
Vitamin A (as palmitate)	150 mcg RAE (500 IU)	17%
Vitamin C (as calcium ascorbate, potassium ascorbate)	15 mg	17%
Vitamin D3 (as cholecalciferol)	1.25 mcg (50 IU)	6%
Vitamin E (as d-alpha tocopheryl acetate)	5 mg (10 IU)	33%
Vitamin K2 (as menaquinone-7)	15 mcg	13%
Vitamin B1 (as thiamin hydrochloride)	0.5 mg	42%
Vitamin B2 (as riboflavin-5'-phosphate)	0.5 mg	38%
Vitamin B3 (as niacinamide)	2.5 mg	16%
Vitamin B6 (as pyridoxal-5'-phosphate)	1 mg	59%
Folate (as L-5-Methyltetrahydrofolic acid, calcium salt)	68 mcg DFE	17%
Vitamin B12 (as methylcobalamin)	0.8 mcg	33%
Biotin	10 mcg	33%
Pantothenic Acid (as d-calcium pantothenate)	2.5 mg	50%
Calcium (as calcium ascorbate, calcium citrate)	50 mg	4%
Iron (as ferrous gluconate)	0.5 mg	3%

	Amount Per Serving	%Daily Value
Phosphorus (as sodium phosphate)	100 mg	8%
Iodine (as potassium iodide)	15 mcg	10%
Magnesium (as magnesium malate)	25 mg	6%
Zinc (as zinc citrate)	1.5 mg	14%
Selenium (as L-selenomethionine)	15 mcg	27%
Copper (as copper sulfate)	0.1 mg	11%
Manganese (as manganese citrate)	0.2 mg	9%
Molybdenum (as sodium molybdate)	7.5 mcg	17%
Sodium (as sodium phosphate)	148.5 mg	6%
Potassium (as potassium citrate, potassium ascorbate)	100 mg	2%
Choline (as choline bitartate)	25 mg	5%
Proprietary Essential AA Blend (as Reginator®) (L-Leucine, L-Lysine, L-Valine, L-Isoleucine, L-Arginine, L-Threonine, L-Phenylalanine, L-Methionine, L-Histidine, L-Tryptophan)	1800 mg	**
L-Glutamine	750 mg	**
L-Proline	225 mg	**
L-Aspartic Acid	685 mg	**
L-Serine	410 mg	**
L-Alanine	325 mg	**
Glycine	180 mg	**
L-Tyrosine	40 mg	**
L-Carnitine L-Tartrate	200 mg	**
Taurine	185 mg	**

Percent Daily Values are based on a 2000 calorie diet. ** Daily Value not established.

Other Ingredients: Dextrose monohydrate (non-GMO), medium chain triglycerides (MCT from highly refined coconut oil), tapioca maltodextrin (non-GMO), natural vanilla flavor. **Does not contain gluten.**

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Perspective

Endocrine-Disrupting Chemicals, Gut Microbiota, and Human (In)Fertility—It Is Time to Consider the Triad

Gemma Fabozzi [1,2,*], Paola Rebuzzini [3], Danilo Cimadomo [2,*], Mariachiara Allori [1], Marica Franzago [4,5], Liborio Stuppia [4,6], Silvia Garagna [3,7], Filippo Maria Ubaldi [2], Maurizio Zuccotti [3,7,†] and Laura Rienzi [2,8,†]

1 B-Woman, Via dei Monti Parioli 6, 00197 Rome, Italy
2 Clinica Valle Giulia, GeneraLife IVF, Via De Notaris 2B, 00197 Rome, Italy
3 Laboratory of Developmental Biology, Department of Biology and Biotechnology "Lazzaro Spallanzani", University of Pavia, Via Ferrata 9, 27100 Pavia, Italy
4 Center for Advanced Studies and Technology (CAST), University "G. d'Annunzio" of Chieti-Pescara, 66100 Chieti, Italy

Fabozzi G et al. Endocrine-disrupting chemicals, gut microbiota, and human (In)fertility – It is time to consider the triad, *Cells*, Vol. 11, No. 3335, 2022.

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Citation: Fabozzi, G.; Rebuzzini, P.; Cimadomo, D.; Allori, M.; Franzago, M.; Stuppia, L.; Garagna, S.; Ubaldi, F.M.; Zuccotti, M.; Rienzi, L. Endocrine-Disrupting Chemicals, Gut Microbiota, and Human (In)Fertility—It Is Time to Consider the Triad. *Cells* **2022**, *11*, 3335. https://doi.org/10.3390/cells11213335

Abstract: The gut microbiota (GM) is a complex and dynamic population of microorganisms living in the human gastrointestinal tract that play an important role in human health and diseases. Recent evidence suggests a strong direct or indirect correlation between GM and both male and female fertility: on the one hand, GM is involved in the regulation of sex hormone levels and in the preservation of the blood–testis barrier integrity; on the other hand, a dysbiotic GM is linked to the onset of pro-inflammatory conditions such as endometriosis or PCOS, which are often associated with infertility. Exposure to endocrine-disrupting chemicals (EDCs) is one of the main causes of GM dysbiosis, with important consequences to the host health and potential transgenerational effects. This perspective article aims to show that the negative effects of EDCs on reproduction are in part due to a dysbiotic GM. We will highlight (i) the link between GM and male and female fertility; (ii) the mechanisms of interaction between EDCs and GM; and (iii) the importance of the maternal–fetal GM infertility. Whilst this dysregulation of EDCs on the GM is evident during adult life, we will suggest that it might occur also during the early post-natal phases of life and fetal development, speculating, for the latter, a possible transgenerational effect.

"Whilst this dysregulation of endocrine disrupting chemicals (EDCs) on the gut microbiota is evident during adult life, we will suggest that it might occur also during the early post-natal phases of life and fetal development, speculating, for the latter, a possible transgenerational effect."

2. Gut Microbiota: A New Player in Town

The GM is a complex and dynamic population of microorganisms living in the human gastrointestinal tract that exerts biochemical functions otherwise absent in the host. GM is

Microbiota and infant development

- "…increasing evidence suggests that the acquisition and development of a healthy microbiota in the infant are pivotal to exerting long-lasting beneficial effects in disease prevention."
- "The maternal microbial reservoir is crucial in the maternal-to-infant passage."

Microbiota and infant development

- “Maternal vaginal, oral, gut, skin, and breast milk microbial communities contribute to establishing the infant’s own gut microbial community, thus regulating correct fetal growth, neurodevelopment, and immune programming and providing a prophylactic potential of non-communicable diseases, such as obesity, immunoinflammatory disorders, and neurocognitive complications.”

The nature of microbial colonization of the infant

- “Extensive microbial colonization takes place post-partum through the mode of delivery, contact with the mother (such as skin-to-skin care), maternal diet, and breastfeeding; however, gut colonization might occur already during the prenatal period.”

The nature of microbial colonization in the infant

- “Recent, although controversial, findings question the dogma that the womb is sterile, suggesting that the fetus incorporates an initial microbial inoculum already before birth (in utero colonization hypothesis), followed by postnatally supplemented maternal microbes.”

How do EDCs interact with the gut microbiota?

It's somewhat of a vicious circle

- "On the one hand, environmental contaminants alter gastrointestinal bacteria composition and/or the metabolic activity that shapes the host's microbiotype; on the other hand, gut microbiota extensively metabolizes environmental chemicals, thus modulating their toxicity in the host."

Gut microflora is a detoxification organ

- “Indeed, the microbiota is pictured as an additional organ involved in xenobiotic transformation and influencing the pharmacokinetics of environmental chemicals. Therefore, an altered symbiotic flora may differentially modulate chemical toxicity.”

How do EDCs and gut microbiota interact: Through direct and indirect metabolism

- "…xenobiotics enter the human body mainly through the gastrointestinal tract and reach the distal gut where they can be directly metabolized by gut microbiota performing diverse chemical transformations such as hydrolysis, removal of the succinate group, dihydroxylation, acetylation, deacetylation, proteolysis, denitration, deconjugation, or thiazole ring opening."

How do EDCs and gut microbiota interact: Through direct and indirect metabolism

- “In other circumstances, after ingestion, xenobiotics such as the non-polar ones are transported to the liver for detoxification where they are oxidized and subsequently eliminated in urine or secreted into the bile. In the latter case, they move to the small intestine where they can be absorbed, or they progress down to the large intestine where they are metabolized by the gut microbiota.”

How do EDCs and gut microbiota interact: By altering microbial diversity and inducing dysbiosis

- "…it has been has been demonstrated that both bisphenol A and ethinylestradiol exposure can elevate the amount of *Bifidobacterium* spp. in mice, leading to metabolic disorders; instead, methylparaben, diethyl phthalate, and triclosan (or their mixture) exposure modifies, in rats, the ratio between *Bacteroidetes* and *Firmicutes* spp., a relevant marker of gut dysbiosis."

How do EDCs and gut microbiota interact: By altering microbial diversity and inducing dysbiosis

- “Moreover, EDCs reduce the number of microbial species such as *Lactobacillus* spp., important for xenobiotic biotransformation and involved in the maintenance of a proper intestinal barrier, thus resulting in the enhanced absorption of contaminants and toxicity to the host.”

How do EDCs and gut microbiota interact: By interfering with gut microbiota enzymatic activity

- "…gut microbiota significantly contributes to the host metabolism by providing enzymes encoded by the gut microbiome (i.e., the genome of gut microbiota) which are involved in both the xenobiotic and endobiotic metabolism.

How do EDCs and gut microbiota interact: By interfering with gut microbiota enzymatic activity

- “Among the most important of these enzymes, β-glycosidase catalyzes the hydrolysis of plant polyphenol glycosides, and β-glucuronidase catalyzes the removal of glucuronic acid from liver-produced glucuronides. Consequently, EDCs, by perturbating gut microbiota, may alter host physiological processes mediated by these enzymes.”

Gut microflora and female fertility

Gut microbiota and sex hormone levels

- "…the gut microbiome encodes different enzymes involved in host metabolism, and one of them, the enzyme β-glucuronidase, is responsible for the metabolism and modulation of circulating estrogen hormones since it deconjugates estrogens, enabling their binding to estrogen receptors and leading to physiological downstream effects."

Gut microbiota and sex hormone levels

- “Therefore, changes to the microbial population encoding the enzyme β-glucuronidase…affect the endogenous estrogen metabolism by modulating the enterohepatic circulation of these hormones, with a subsequent impact on the woman’s hormonal balance and, therefore, on her fertility.”

Gut microbiota and metabolic influences on fertility

- "…a dysbiotic gut microbiota is observed in several infertility-related disorders such as endometriosis, polycystic ovary syndrome (PCOS), insulin resistance, and obesity, characterized by an unbalanced immune profile and pro-inflammatory status, known to negatively affect fertility."

Gut microbiota and metabolic influences on fertility

- “All these conditions are characterized by a reduced gut microbiota biodiversity and specific microbial imbalances in both the gut and reproductive tract leading to immune dysfunction, compromised immunosurveillance, and altered immune cell profiles.”

Gut microflora and other microbial populations

- “Gut microbiota…plays a key role in female fertility since it has been demonstrated that gut microbiota can influence the whole genital tract microbiota through continuous crosstalk between uterus and vagina ecosystems.”

Gut microflora and other microbial populations

- ***"Therefore, a condition of dysbiosis in the gut could possibly lead to vaginal and uterine dysbiosis, negatively affecting endometrial receptivity at the time of implantation."***

Gut microflora, leaky gut, and vaginal microflora

- "…gut microbiota dysbiosis can induce the leaky-gut syndrome leading to intestinal permeability and leakage of bacteria and bacterial products from the gut into the circulation, thus affecting the female genital tract microbiota."

EDCs, gut microflora and female reproductive health: Putting it all together

The fetus is more susceptible to adverse sequelae from chemical exposure compared to adults

The fetus and exposure to chemicals

- “EDC exposure during adulthood has been clearly associated with negative effect for human health; however, EDC exposure in both pre- and post-natal periods may exert even worse consequences:”

The fetus and exposure to chemicals

- “Firstly, because in this phase the human gut is much less resilient and much more responsive to external and environmental factors than the adult gut.”
- “Indeed, fetuses are exposed to a greater risk than adults from food contaminants due to their higher absorption rate, poor detoxification and elimination capacity, faster cell proliferation, and the still immature DNA repair mechanism.”

Immaturity of the perinatal neonatal microflora

The perinatal and neonatal gut microflora

- ***"Secondly, because during the perinatal and neonatal period, the microbial ecosystem inside undergoes an unprecedented process of shaping."***

The net result

- “Therefore, any disturbance in this timeframe may lead to more detrimental effects than at any other moment in life affecting both acquisition and constitution of a healthy gut microflora, with subsequent implications for the exposed individual, offspring health, and their reproductive capacity.”

EDCs, dysbiosis and epigenetic programming

- “EDCs inducing gut microbiota dysbiosis may induce a downstream effect on epigenetic programming and regulation with critical consequences if occurring during the first 1000 days of life of a human individual, a period in which epigenetic DNA imprinting activity is most active and different factors such as nutrition, microbiome, and epigenome play a key role in developmental programming, influencing susceptibility to the development of diseases later in life.”

Possible clinical implications

- “In the era of precision medicine, a better understanding of the role of gut microbiota in reproduction opens the possibility to develop novel strategies to prevent or treat infertility and the diseases associated with it, such as maternal dietary modification, probiotic and prebiotic supplementation, and fecal microbiota transplantation.”

Possible clinical implications

- ***"Moreover, the recent correlation between microbiota composition and host epigenome suggests that enrichment for certain microbial species could modulate unique gene expression signatures."***

Gut microbiome and female reproductive issues

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Review

The Gut Microbiome and Female Health

Ruqaiyyah Siddiqui [1,2], Zinb Makhlouf [1], Ahmad M. Alharbi [3], Hasan Alfahemi [4] and Naveed Ahmed Khan [2,5,*]

1 College of Arts and Sciences, American University of Sharjah, University City, Sharjah 26666, United Arab Emirates
2 Department of Medical Biology, Faculty of Medicine, Istinye University, Istanbul 34010, Turkey
3 Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Taif University, Taif 21944, Saudi Arabia
4 Department of Medical Microbiology, Faculty of Medicine, Al-Baha University, Al-Baha 65799, Saudi Arabia
5 Department of Clinical Sciences, College of Medicine, University of Sharjah, University City, Sharjah 27272, United Arab Emirates
* Correspondence: naveed5438@gmail.com

Siddiqui R et al. The gut microbiome and female health, *Biology,* Vol. 11, 2022

certain bacterial species should be considered, as novel independent or adjunct therapies for various female-related pathologies. Strategies such as the modulation of the gut microbiome via diet and through supplementation with pre/pro/postbiotics in various female health-related issues should be undertaken.

Abstract: The possession of two X chromosomes may come with the risk of various illnesses, females are more likely to be affected by osteoarthritis, heart disease, and anxiety. Given the reported correlations between gut microbiome dysbiosis and various illnesses, the female gut microbiome is worthy of exploration. Herein, we discuss the composition of the female gut microbiota and its dysbiosis

Citation: Siddiqui, R.; Makhlouf, Z.; Alharbi, A.M.; Alfahemi, H.; Khan, N.A. The Gut Microbiome and Female Health. *Biology* **2022**, *11*, 1683. https://doi.org/10.3390/biology11111683

"Interestingly, an investigation of gut microbiota changes in patients with positive immune antibody-associated miscarriage reveals that some highly abundant genera, such as *Blautia* and *Bacteroides*, may be incriminated in recurrent miscarriage."

iations.

lactis W58 alleviated vascular malfunction and arterial stiffness in obese postmenopausal women, and finally, while further research is needed, *Prevotella* maybe protective against postmenopausal bone mass loss. As several studies report the therapeutic potential of probiotics and since the gut microbiota of certain female pathological states has been relatively characterized, we speculate that the administration of certain bacterial species as probiotics is warranted, as novel independent or adjunct therapies for various female pathologies.

Keywords: gut microbiota; estrobolome; estrogen; probiotic; gut dysbiosis

Microbiome and pregnancy

- “Notably, profound alterations in the microbial profile of the gut microbiome have been observed during the progression of pregnancy such as an increase in *Actinobacteria*, *Proteobacteria,* and opportunistic pathogens, and a decrease in SCFA producers and in overall species richness.”

Microbiome and pregnancy

- "In humans, an analysis of the gut microbiome of thirty-five women in their first and third trimesters of pregnancy reveals that *Bifidobacterium*, *Blautia,* unclassified *Ruminococcacae*, *Bacteroides*, unclassified *Lachnospiraceae*, unclassified *Clostridiales*, *Akkermansia, Faecalibacterium, Ruminococcus,* and *Prevotella* were generally dominant bacterial species."

Microbiome and pregnancy

- “Interestingly, *Bifidobacterium* is crucial for human milk oligosaccharide degradation and *Prevotella* metabolizes estradiol and progesterone.”
- “Differences were also observed between the two semesters.”

Microbiome and pregnancy

- “Furthermore, *Bifidobacterium*, Neisseria, Blautia, and *Collinsella*, increased most significantly in the third semester while *Dehalobacterium, Clostridium*, and *Bacteroidales* were markedly higher in the first.”
- “Another report disclosed that maternal microbiome biodiversity changes with the progression of pregnancy and is associated with gestational weight gain.”

Gut microbiome and the menstrual cycle according to Siddiqui et al.

Reproductive hormones and β-glucuronidase

- “A decrease in the gut microbiome diversity affects β-glucuronidase activity adversely, lowering estrogen levels.”
- “Since estrogen is only biologically active if deconjugated, this deconjugation enables estrogen to bind to its receptors: estrogen receptor alpha and estrogen receptor beta.”

Reproductive hormones and β-glucuronidase

- “Estrogen is crucial for homeostasis in healthy premenopausal women and its decrease accompanying menopause drives metabolic rate reduction and weight gain, yet it also stimulates epithelial proliferation within the female reproductive tract, driving various proliferative diseases such as uterine fibroids and endometriosis.”

Reproductive hormones and β-glucuronidase

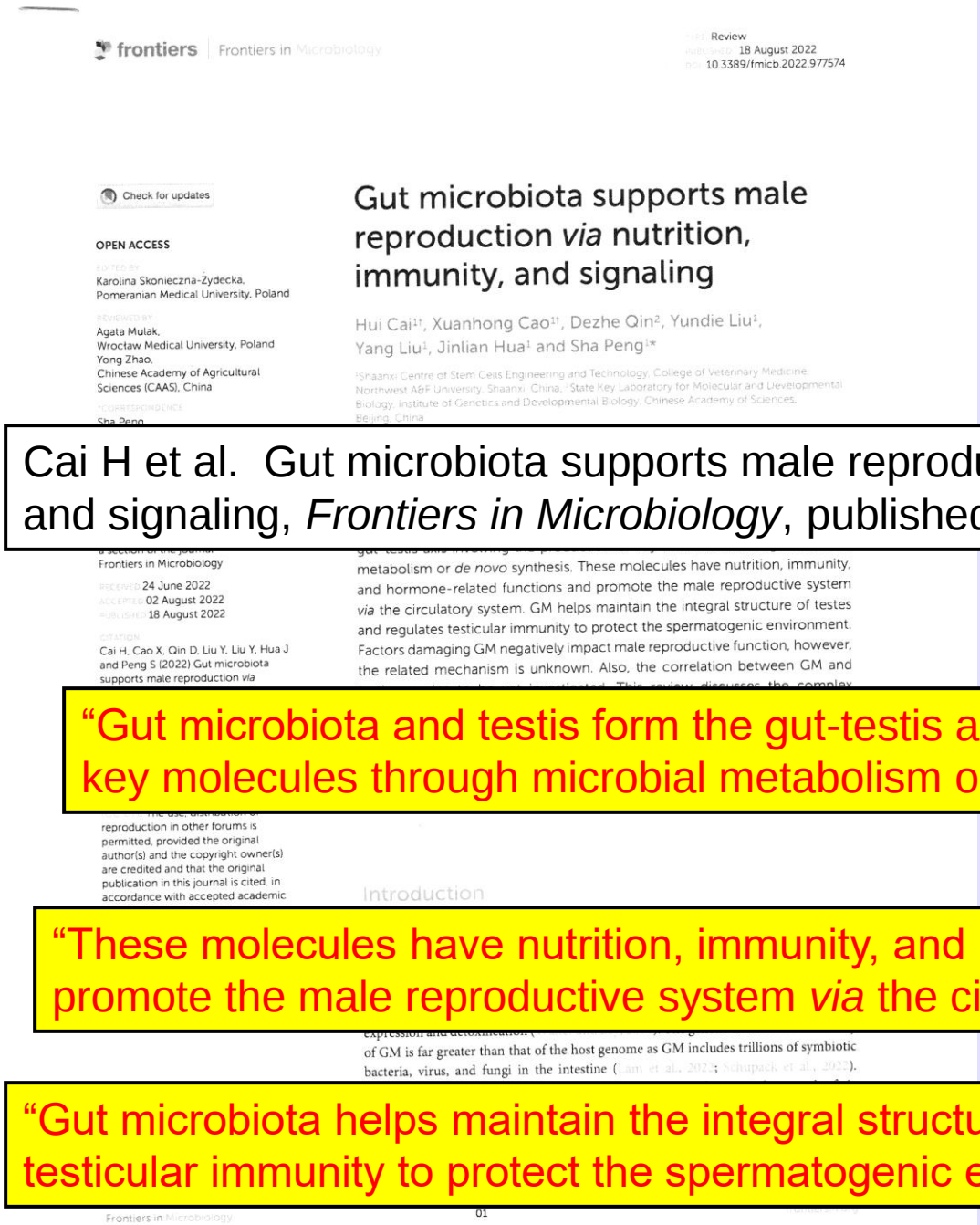
- “This engendered the hypothesis that the gut microbiome of endometriosis patients may have higher densities of β-glucuronidase producing bacteria than the controls.”
- “In fact, a study reported that gut microbiota alterations were observed in the rhesus monkey model of endometriosis, namely, fewer *Lactobacilli* shedding in feces.”

Microbiota and the menstrual cycle

- “A study reports a lack of significant menstruation-driven changes in the saliva and fecal microbiomes, yet discloses an increased diversity in the vaginal microbiome during menses, which is ensured by an expansion of *Lactobacillus* during the follicular and luteal phases.”

Microbiota and the menstrual cycle

- “Similarly, another recent study reports increased vaginal microbial diversity and a correlation between *Lactobacillus* abundances and predicted estradiol levels across the menstrual cycle.”
- “Analysis of the oral microbiome were also carried out. Interestingly, anaerobic bacterial counts in saliva are reported to increase during ovulation.”



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Review
18 August 2022
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18 August 2022

Cai H, Cao X, Qin D, Liu Y, Liu Y, Hua J and Peng S (2022) Gut microbiota supports male reproduction *via*

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Introduction

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01

Gut microbiota supports male reproduction *via* nutrition, immunity, and signaling

Hui Cai[1†], Xuanhong Cao[1†], Dezhe Qin[2], Yundie Liu[1], Yang Liu[1], Jinlian Hua[1] and Sha Peng[1*]

[1]Shaanxi Centre of Stem Cells Engineering and Technology, College of Veterinary Medicine, Northwest A&F University, Shaanxi, China, [2]State Key Laboratory for Molecular and Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China

metabolism or *de novo* synthesis. These molecules have nutrition, immunity, and hormone-related functions and promote the male reproductive system *via* the circulatory system. GM helps maintain the integral structure of testes and regulates testicular immunity to protect the spermatogenic environment. Factors damaging GM negatively impact male reproductive function, however, the related mechanism is unknown. Also, the correlation between GM and

of GM is far greater than that of the host genome as GM includes trillions of symbiotic bacteria, virus, and fungi in the intestine (

Cai H et al. Gut microbiota supports male reproduction *via* nutrition, immunity, and signaling, *Frontiers in Microbiology*, published online August 18, 2022

"Gut microbiota and testis form the gut-testis axis involving the production of key molecules through microbial metabolism or *de novo* synthesis."

"These molecules have nutrition, immunity, and hormone-related functions and promote the male reproductive system *via* the circulatory system.

"Gut microbiota helps maintain the integral structure of testes and regulates testicular immunity to protect the spermatogenic environment."

Take away message

- No matter what the issue is clinically when addressing human reproductive concerns:

DON'T FORGET TO ADDRESS THE GUT

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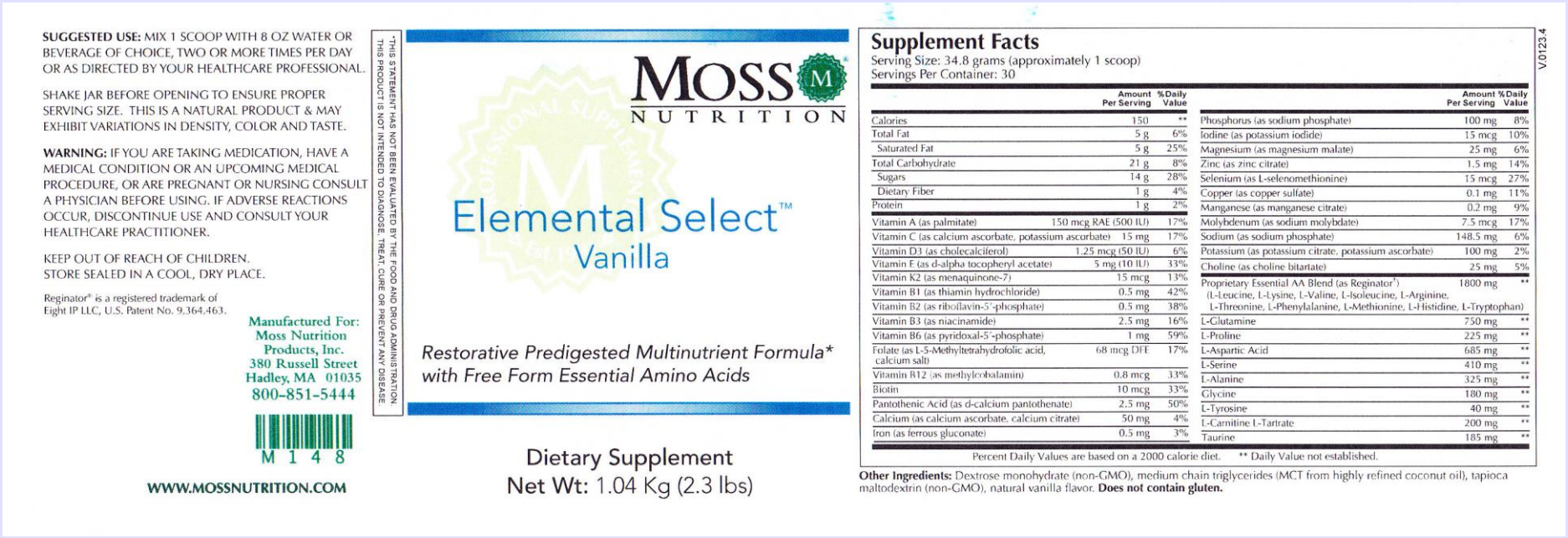

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Dietary Supplement
Net Wt: 1.04 Kg (2.3 lbs)

Supplement Facts

Serving Size: 34.8 grams (approximately 1 scoop)
Servings Per Container: 30

	Amount Per Serving	%Daily Value
Calories	150	**
Total Fat	5 g	6%
Saturated Fat	5 g	25%
Total Carbohydrate	21 g	8%
Sugars	14 g	28%
Dietary Fiber	1 g	4%
Protein	1 g	2%
Vitamin A (as palmitate)	150 mcg RAE (500 IU)	17%
Vitamin C (as calcium ascorbate, potassium ascorbate)	15 mg	17%
Vitamin D3 (as cholecalciferol)	1.25 mcg (50 IU)	6%
Vitamin E (as d-alpha tocopheryl acetate)	5 mg (10 IU)	33%
Vitamin K2 (as menaquinone-7)	15 mcg	13%
Vitamin B1 (as thiamin hydrochloride)	0.5 mg	42%
Vitamin B2 (as riboflavin-5'-phosphate)	0.5 mg	38%
Vitamin B3 (as niacinamide)	2.5 mg	16%
Vitamin B6 (as pyridoxal-5'-phosphate)	1 mg	59%
Folate (as L-5-Methyltetrahydrofolic acid, calcium salt)	68 mcg DFE	17%
Vitamin B12 (as methylcobalamin)	0.8 mcg	33%
Biotin	10 mcg	33%
Pantothenic Acid (as d-calcium pantothenate)	2.5 mg	50%
Calcium (as calcium ascorbate, calcium citrate)	50 mg	4%
Iron (as ferrous gluconate)	0.5 mg	3%

	Amount Per Serving	%Daily Value
Phosphorus (as sodium phosphate)	100 mg	8%
Iodine (as potassium iodide)	15 mcg	10%
Magnesium (as magnesium malate)	25 mg	6%
Zinc (as zinc citrate)	1.5 mg	14%
Selenium (as L-selenomethionine)	15 mcg	27%
Copper (as copper sulfate)	0.1 mg	11%
Manganese (as manganese citrate)	0.2 mg	9%
Molybdenum (as sodium molybdate)	7.5 mcg	17%
Sodium (as sodium phosphate)	148.5 mg	6%
Potassium (as potassium citrate, potassium ascorbate)	100 mg	2%
Choline (as choline bitartate)	25 mg	5%
Proprietary Essential AA Blend (as Reginator®) (L-Leucine, L-Lysine, L-Valine, L-Isoleucine, L-Arginine, L-Threonine, L-Phenylalanine, L-Methionine, L-Histidine, L-Tryptophan)	1800 mg	**
L-Glutamine	750 mg	**
L-Proline	225 mg	**
L-Aspartic Acid	685 mg	**
L-Serine	410 mg	**
L-Alanine	325 mg	**
Glycine	180 mg	**
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Taurine	185 mg	**

Percent Daily Values are based on a 2000 calorie diet. ** Daily Value not established.

Other Ingredients: Dextrose monohydrate (non-GMO), medium chain triglycerides (MCT from highly refined coconut oil), tapioca maltodextrin (non-GMO), natural vanilla flavor. **Does not contain gluten.**

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