Article

The Importance of Dietary Fiber on Stress Hormone in Pregnancy: A Literature Review

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A B S T R A C T

Antepartum depression is a mental health issue that is frequently ignored and often leads to suicidal behaviours. The harmful effects of antepartum depression are not only experienced by mothers, but also by children in the future. Depression due to pregnancy is usually attributed to several causes, including the biological component. Biological shifts that arise during gestation interrupt the maternal stress protection mechanism, one of which is the dysregulation of the hypothalamus-pituitary-adrenal axis (HPA-axis) resulting in hypersecretion of cortisol. Excessive release of cortisol as a stress hormone has been correlated with depressive symptoms, particularly throughout pregnancy. Recently, dietary factors, in particular dietary fiber, have become of concern as component that is recognized to attenuate stress hormones. The dietary fiber that is ingested will be digested by intestinal bacteria and will produce short-chain fatty acids as the essential metabolites. These metabolites are known to play a role in various brain functions, including HPA-axis through various means. The objective of this research is aimed at determining the function of dietary fiber within cortisol as a biomarker of the central stress response system, particularly throughout pregnancy.

I. INTRODUCTION

One out of 10 women across the world struggled with depression during pregnancy. Predominantly, in developing countries, such occurrence is found to be 1.5 times higher(WHO, 2015). Depression that develops during pregnancy or hereafter oftentimes named as antepartum depression does not only cause detrimental effects during pregnancy on maternal health, but also affects the infant in the present, including impaired cognitive and socio-emotional growth, and low immune function(Orta *et al.*, 2017; Rackers *et al.*, 2017; Osborne *et al.*, 2018; Szpunar and Parry, 2018). Depression is a severe type of stress that is persistent and cannot be controlled by stress defense mechanisms(Orta *et al.*, 2017). If stress is established, both physical or emotional, the body responds by transmitting information to the brain to induce the HPA-axis signaling pathway. The axis generated by the neural cascade and endocrine signals passes from the brain to the adrenal cortex which stimulates cortisol release as the result (Gropper and Smith, 2013; Dominiczak, Beastall and Wallace, 2014).

Cortisol refers to a type of glucocorticoid hormone that is used to brace the body for extreme stress situations. Once performs circulation, cortisol can act as a negative feedback mechanism on the HPA-axis to inhibit cortisol secretion(Gropper and Smith, 2013; Dominiczak, Beastall and Wallace, 2014). Throughout pregnancy, biological changes occur that impair the defense functions of the mother's stress. The progression of the placenta as a major endocrine organ, which secretes placental corticotropin-releasing hormone (CRH), will lead to a dramatic rise in the secretion of cortisol. Peculiarly, this excessive secretion of cortisol does not constitute a negative feedback signal, but rather causes the HPA-axis to deregulate due to failure of the feedback system and hypersecretion of cortisol. This situation is typically associated with symptoms of depression, including during pregnancy(Seth, Lewis and Galbally, 2016; Rackers *et al.*, 2017).

Multiple aspects can raise the extent of cortisol in the body, one of which is a dietary habit. Dietary fiber is one of the priorities at the moment. Dietary fiber is an integral part of food sources composed of carbohydrates and is immune to digestive enzymes such that it cannot be hydrolyzed or consumed in the small intestine (Zielinski *et al.*, 2013). Throughout the large intestine, intestinal microbiota will ferment and contain metabolites such as acetate, propionate, and butyrate, known as short-chain fatty acid (SCFA). Such fermented fiber product is classified to regulate brain function, including HPA-axis, through the use of the intestinal brain axis(Rea, Dinan and Cryan, 2016; Sampson and Mazmanian, 2017; Dalile *et al.*, 2019). At present, the importance of dietary fiber during pregnancy, primarily against stress hormones, has not been widely researched. The purpose of this research is to investigate the mechanism of the role of dietary fiber in cortisol as a predictor of the HPA-axis function in pregnancy.

II. DISCUSSION

Dietary Fiber as a Substrate in the Process of Forming Short Chain Fatty Acids

Dietary fiber is a carbohydrate polymer composed of 10 or more monomeric units that cannot be hydrolyzed by digestive enzymes in the small intestine. Generically, premised on their chemical, physical, and functional properties, the fibers can be divided into two categories, namely soluble fiber and insoluble fiber (Table 1) (Lattimer and Haub, 2010).Such two forms of fiber are respectively found in products containing 1/3 soluble fiber and 2/3 insoluble fiber. Nutrients high in soluble fiber include legumes (nuts, lentils), vegetables (cabbage, mustard greens), fruit (apples, berries, pears), wheat germ, psyllium seeds, barley, oats, and many others. Although linseeds, whole grains, dairy products, vegetables (celery, carrots) are food sources of insoluble fiber (Lattimer and Haub, 2010; Sharma *et al.*, 2016). Fiber specifications, both soluble and insoluble, must be fulfilled regularly. The average fiber consumption for women of childbearing age is 25-30 grams per day with a rise of 3-4 grams per day during pregnancy(FDA, 2018; Kementerian Kesehatan RI, 2019).

For digestion, fiber is used as a medium for the hydraulic process by enzymes formed by intestinal bacteria throughout the fermentation cycle in the large intestine. This cycle will produce numerous metabolites such as SCFA, CO_2, H_2, CH_4, and H_2S (Caprita *et al.*, 2010).The variation in SCFA depends on the particular medium and the group of microorganisms involved, but in principle, the most common products contained in feces are acetate, propionate, and butyrate with an average molar concentration of 3:1:1 (Caprita *et al.*, 2010; Holscher, 2017). This stimulatory relationship between the fibers and the intestinal bacteria is expected to increase the central nervous system, particularly the HPA-axis, along the intestinal-brain axis. The intestinal brain axis is a bi-directional transmission network

between the intestines, intestinal bacteria, and the brain spanning the vagal network, immune system regulators, hormones, bacterial metabolites such as SCFA, and neurotransmitters (Mohajeri *et al.*, 2018). SCFA metabolites produced from fiber fermentation can influence the control of the HPA-axis by the intestinal brain axis, whether intentionally or unintentionally(Christian *et al.*, 2016; Dalile *et al.*, 2019). Thus dietary fiber consumption must be met, as studies have shown that low fiber consumption can be linked to higher pathogenic bacteria and reduced SCFA development(Clark and Mach, 2016).

Table 1. Dietary fiber classification based on solubility.

Type of Fiber	Principal chemical content	Main physiological outcomes
Soluble Fiber	Beta glucan, fructan, gum, pektin, mucilage	Forms a gel to increase transit time and slow gastric emptying, easily fermented by intestinal bacteria, functioned as prebiotic and produces short chain fatty acid
Insoluble Fiber	Selulose, hemiselulose, lignin	Expedites intestinal transit time, has a laxative effect by forming dense feces, less fermented by intestinal bacteria

Data Source: (Caprita *et al.*, 2010)

Impacts of Dietary Fiber Metabolites on Stress Hormone Regulation in Pregnancy

Local and systemic inflammation stimulates the release of cortisol by the central nervous system as well as the HPA-axis. Local inflammation that arises in the intestine plays an important part in neuroinflammation by bringing coordination among the enteric nervous system and the central nervous system to further be mediated by the vagus nerve. Inflammatory mediators within the intestine will stimulate the afferent nerve ends of the vagus nerves, and transmit a signal to the brain to activate defensive cells in the brain(Rea, Dinan and Cryan, 2016; Dalile *et al.*, 2019). While local inflammation plays a large part in neuroinflammation through the vagal mechanism, systemic inflammation directly stimulates immune cells in the brain. Immune cells in the brain, namely microglia, serve as the primary inhibitor of the neuroinflammation cycle. Once engaged, microglia release multiple cytokines and chemokines, control other neurotransmitters, which in turn stimulate the HPA-axis and increase the secretion of cortisol(Rea, Dinan and Cryan, 2016).

In addition to the brain and intestines, this inflammatory response also accelerates the enzymatic activity of indoleamine 2,3-dioxygenase, which plays a vital role throughout the metabolism of tryptophan within the liver. Moreover, accelerated tryptophan metabolism can induce a reduction in the development of serotonin or 5-hydroxytryptamine (5-HT) as it is acknowledged that tryptophan is a type of amino acid that functions as a precursor to 5-HT. This reduction in 5-HT will enhance the levels of the HPA-axis in the brain and through the vagal pathway. Research has demonstrated that a drop in 5-HT in people with mental-emotional problems causes the rise of cortisol levels(Rea, Dinan and Cryan, 2016; Dalile *et al.*, 2019).

SCFA affects the HPA-axis by attenuating local and systemic inflammatory mechanisms through certain immune pathways(Rea, Dinan and Cryan, 2016; Dalile *et al.*, 2019). The exercise of SCFA and immune cells in the intestine that indirectly minimize local and systemic inflammation by improving the intestinal barrier and blocking the diffusion of bacteria and bacterial products, including microbial-associated molecular patterns (MAMPs) such as lipopolysaccharide (LPS), bacterial lipoprotein (BLP) and flagellin, which may damage proteins within intestinal barrier(Rea, Dinan and Cryan, 2016; Sampson and Mazmanian, 2017; Dalile *et al.*, 2019). SCFA also regulates the diversification, mobilization, and activation of neutrophils, dendritic cells, macrophages, monocytes, and T cells. SCFA also prevents the aging process and development of proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-12 (IL-12)(Dinan and Cryan, 2012; Dalile *et al.*, 2019). SCFAs also play a critical part in the identity and viability of microglia, which decreases inhibition of the HPA-axis(Rea, Dinan and Cryan, 2016).

Within hormonal cascade, SCFAs can attenuate the secretion of the digestive hormones that influence the modulation of the HPA-axis. Receptors that induce the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) from enteroendocrine L intestinal cells are triggered by SCFA. These two

hormones play a significant role in the modulation of the axis by enabling systemic circulation or providing signals through the vagal pathway(Farzi, Fröhlich and Holzer, 2018).The administration of GLP-1, in the long run, resulted in an antidepressant activity and diminished cortisol in mice(Farzi, Fröhlich and Holzer, 2018; Dalile *et al.*, 2019). While, PYY is an anorexic neuropeptide that is found in specific areas of the brain, mainly in the hypothalamus and pituitary gland. The PYY hormone will affect the central nervous system if the transmitting hormone passes the blood-brain barrier or inhibits the nerves of the vagus nerves. The research that eliminated the PYY coding gene in mice prompted an exacerbation of depression and anxiety. It is established from these studies that PYY can play a central role in the modulation of the HPA-axis(Rea, Dinan and Cryan, 2016; Farzi, Fröhlich and Holzer, 2018; Dalile *et al.*, 2019).

Some other hormones that affect the modulation of the HPA-axis are leptin and ghrelin. Leptin is a nor exogenous hormone that secretes adipocyte cells and acts through receptors in the hypothalamus. In a diet rich in fat and low in carbohydrates, there is adherence to leptin receptors in the hypothalamus that induces HPA-axis dysregulation(Farzi, Fröhlich and Holzer, 2018), As with ghrelin, SCFA is reported to lower ghrelin levels in plasma. The mechanism of the inverse interaction between SCFAs and Ghrelin remains uncertain. However, numerous studies have suggested that ghrelin impacts the activity of the brain by systemic inflammation and the vagus nerve. The role of ghrelin in axis control was demonstrated in a study in mice that lacked the ghrelin coding gene. In the absence of ghrelin, the negative feedback system of the axis is impaired and the secretion of cortisol is unnecessary(Farzi, Fröhlich and Holzer, 2018; Dalile *et al.*, 2019).

The intestinal-brain axis also contains the vagal system in attenuating the activity of the HPA-axis. The enteric nervous system, embodied by the vagus nerve, can detect signals through the absorption of contaminants or bacterial products that traverse the intestinal barrier such as LPS, 5-HT and gamma-aminobutyric acid (GABA) and hormones ingested by intestinal enteroendocrine L cells, even when they're not in close interaction with intestinal bacteria or lumen material. Signals collected by the nociceptive end of the vagus nerve will trigger the release of neurotransmitters in the brain and directly impact brain function, along with the HPA-axis(Rea, Dinan and Cryan, 2016; Sampson and Mazmanian, 2017; Dalile *et al.*, 2019). Animal studies on the influence of SCFA on the vagus nerve have shown that the treatment of SCFA in the form of sodium butyrate provokes the response of the vagus nerve afferent fibers. If the reaction is delayed, the nerve ablation or desensitization of the nerves would be performed by capsaicin(Dalile *et al.*, 2019).

One way for SCFA to impact the central nervous system is immediately influencing the humoral system of the brain. The blood-brain barrier is an essential component in determining the homeostasis's central nervous system where SCFA performs a role in maintaining the quality of the blood-brain barrier so that the removal of bacteria and their products can be restricted. Propionic acid is established to shield the blood-brain barrier from bacterial products such as LPS that may disrupt close junctions made up of proteins such as occludin, claudin-5, and zone occludens-1. Once a cohesion of these tight joints is compromised, the diffusion of bacteria and their products can lead to inflammation within the brain, which in turn triggers the HPA-axis(Sampson and Mazmanian, 2017).Research indicates that SCFAs can also traverse the blood-brain barrier and have neuroprotective roles. The role of dietary fiber to affect brain activity often includes neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF). These proteins control the development, preservation, and segregation of neurons and synapses in the central and peripheral nervous systems(Dalile *et al.*, 2019). BDNF plays a crucial role in follicular growth, placenta, and implantation during pregnancy. Nonetheless, this protein declines during pregnancy and is strongly correlated with depressive symptoms throughout pregnancy(Christian *et al.*, 2016).

Research in animals and human studies have indicated a connection linking dietary fiber and the stress response. Schmidt et al. 's intervention test in stable individuals showed that the use of galactooligosaccharide (GOS) would decrease salivary cortisol levels relative to placebo(Schmidt *et al.*, 2015). Sugiyama et al. have reported that fiber intake reduced the levels of salivary cortisol in athletes relative to placebo(Sugiyama *et al.*, 2017). However, separate findings were observed in experiments in a group of stable participants that obtained a high-fiber diet in the absence of substantial variation in salivary cortisol levels relative to controls(Lemmens *et al.*, 2011). Animal testing has shown that high dietary fiber content can control steroid hormones(Jiang *et al.*, 2019). Fiber, therefore, has the effect of rising BDNF in mice. The pathway for neurogenesis and neuroprotection may be due to higher levels of

messenger ribonucleic acid (mRNA) neurotrophic cells(Dalile *et al.*, 2019). In an animal study using mice that experienced distress-like actions after exposure to neurotoxins, there was a decline in anxiety symptoms and a decline in stress hormones after fructooligosaccharide (FOS) and xylooligosaccharide (XOS) ingestion (Krishna and Muralidhara, 2015; Savignac *et al.*, 2015; Burokas *et al.*, 2017).

Scientific evidence on the importance of dietary fiber on the HPA-axis and cortisol on the intestinal axis is favorable. Nevertheless, most of these trials are experimental animal tests, while current human studies are often very small and contradictory, particularly in special groups such as pregnant women. The gestation period becomes a particular concern due to the dramatic change in cortisol levels and intestinal microbiota structure as diverse from the wider public, in which these changes may influence maternal stress hormones and increase vulnerability to stress(Orta *et al.*, 2017; Mohajeri *et al.*, 2018). The dietary fiber composition and digestive circumstances also have a significant effect on the fermentation of fiber within the intestine, while the dietary fiber structure in each population is known to have different varieties(Miki *et al.*, 2015)

III. CONCLUSION

Dietary fiber is a component of carbohydrates that cannot be digested by digestive enzymes and is processed by intestinal bacteria in the large intestine. The fermentation effects release important metabolites, which include SCFA, that can govern cortisol as an HPA-axis biomarker through four pathways, namely the immune, vagal, hormonal, and humoral pathways. Dietary fiber plays a key role in attenuating HPA-axis dysregulation and avoid unnecessary cortisol secretion through such a pathway. Dietary influences such as dietary fiber can be one of the advancements in controlling stress and avoiding maternity anxiety. However, researches on the association between dietary fiber and stress hormones in pregnancy are relatively low. The future investigation, in particular, regarding the population of pregnant mothers, shall be performed taking into account the biological changes in pregnancy that could have an impact on the maternal stress response system.

REFERENCES

Burokas, A. *et al.* (2017) 'Targeting the microbiota-gut-brain axis: Prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice', *Biological Psychiatry*, 82(7), pp. 472–487.

Caprita, A. *et al.* (2010) 'Dietary fiber : Chemical and functional properties', *Journal of Agroalimentary Processes and Technologies*, 16(4), pp. 406–416.

Christian, L. M. *et al.* (2016) 'Serum brain-derived neurotrophic factor (BDNF) across pregnancy and postpartum: Associations with race, depressive symptoms, and low birth weight', *Psychoneuroendocrinology*, 74(12), pp. 69–76.

Clark, A. and Mach, N. (2016) 'Exercise-induced stress behavior, gut-microbiota-brain axis and diet: A systematic review for athletes', *Journal of the International Society of Sports Nutrition*. Journal of the International Society of Sports Nutrition, 13(1), pp. 1–21.

Dalile, B. *et al.* (2019) *The role of short-chain fatty acids in microbiota–gut–brain communication*, *Nature Reviews Gastroenterology & Hepatology*.

Dinan, T. G. and Cryan, J. F. (2012) 'Regulation of the stress response by the gut microbiota: Implications for psychoneuroendocrinology', *Psychoneuroendocrinology*. Elsevier Ltd, 37(9), pp. 1369–1378.

Dominiczak, M. H., Beastall, G. and Wallace, A. M. (2014) 'Biosynthesis of Cholesterol and Steroids', in Baynes, J. W. and Dominiczak, M. H. (eds) *Medical Biochemistry*. 4th edn. Philadelphia: Saunders Elsevier, pp. 209–211.

Farzi, A., Fröhlich, E. E. and Holzer, P. (2018) 'Gut microbiota and the neuroendocrine system',

Neurotherapeutics. Neurotherapeutics, 15(1), pp. 5–22.

FDA (2018) *U.S. Food and Drug Administration. Nutrition Facts Label, Dietary fiber*, *U.S. Food and Drug Administration*. Available at: https://www.accessdata.fda.gov/scripts/interactivenutritionfactslabel/factsheets/Dietary_Fiber.pdf (Accessed: 16 July 2020).

Gropper, S. and Smith, J. (2013) 'Lipids', in Gropper, S. and Smith, J. (eds) *Advanced Nutrition and Human Metabolism*. 6th edn. Australia: Wadsworth Cengage Learning, pp. 138–140.

Holscher, H. D. (2017) 'Dietary fiber and prebiotics and the gastrointestinal microbiota', *Gut Microbes*, 8(2), pp. 172–184.

Jiang, X. *et al.* (2019) 'Crude fiber modulates the fecal microbiome and steroid hormones in pregnant Meishan sows', *General and Comparative Endocrinology*, 277(6), pp. 141–47.

Kementerian Kesehatan RI (2019) *Angka Kecukupan Gizi*. Jakarta: Kementerian Kesehatan RI.

Krishna, G. and Muralidhara (2015) 'Inulin supplementation during gestation mitigates acrylamide-induced maternal and fetal brain oxidative dysfunctions and neurotoxicity in rats', *Neurotoxicology and Teratology*, 49, pp. 49–58.

Lattimer, J. M. and Haub, M. D. (2010) 'Effects of dietary fiber and its components on metabolic health', pp. 1266–1289.

Lemmens, S. G. *et al.* (2011) 'Influence of consumption of a high-protein vs. high- carbohydrate meal on the physiological cortisol and psychological mood response in men and women', *PLoS ONE*, 6(2).

Miki, T. *et al.* (2015) 'Dietary intake of minerals in relation to depressive symptoms in Japanese employees: The Furukawa Nutrition and Health Study', *Nutrition*, 31(5), pp. 686–690.

Mohajeri, M. H. *et al.* (2018) 'The role of the microbiome for human health: from basic science to clinical applications', *European Journal of Nutrition*. Springer Berlin Heidelberg, 57(1), pp. 1–14.

Orta, O. R. *et al.* (2017) 'The association between maternal cortisol and depression during pregnancy, a systematic review', *Physiology & behavior*, 176(3), pp. 139–148.

Osborne, S. *et al.* (2018) 'Antenatal depression programs cortisol stress reactivity in offspring through increased maternal inflammation and cortisol in pregnancy: The Psychiatry Research and Motherhood – Depression (PRAM-D) Study', *Psychoneuroendocrinology*. Elsevier, 98(December 2017), pp. 211–221.

Rackers, H. *et al.* (2017) 'Emerging literature in the microbiota-brain axis and perinatal mood and anxiety disorders', *Physiology & behavior*, 176(3), pp. 139–148.

Rea, K., Dinan, T. G. and Cryan, J. F. (2016) 'The microbiome: A key regulator of stress and neuroinflammation', *Neurobiology of Stress*. The Authors, 4, pp. 23–33.

Sampson, T. R. and Mazmanian, S. K. (2017) 'Control of brain development, function, and behavior by the microbiome', *Physiology & behavior*, 176(5), pp. 139–148.

Savignac, H. *et al.* (2015) 'Bifidobacteria modulate cognitive processes in an anxious mouse strain', *Behavioural Brain Research*, 287(1 July 2015), pp. 59–72.

Schmidt, K. *et al.* (2015) 'Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers', *Psychopharmacology*, 232(10), pp. 1793–1801.

Seth, S., Lewis, A. J. and Galbally, M. (2016) 'Perinatal maternal depression and cortisol function in pregnancy and the postpartum period: A systematic literature review', *BMC Pregnancy and Childbirth*. BMC Pregnancy and Childbirth, 16(1).

Sharma, S. K. *et al.* (2016) 'Utilization of food processing by-products as dietary, functional, and novel fiber: A review', *Critical Reviews in Food Science and Nutrition*, 56(10), pp. 1647–1661.

Sugiyama, F. *et al.* (2017) 'Effects of fiber supplementation for four weeks on athletic performance in Japanese college athletes: A case study—measurement of the athletic performance, salivary biomarkers of stress, and mood, affect balance', *Health*, 09(03), pp. 556–567.

Szpunar, M. J. and Parry, B. L. (2018) 'A systematic review of cortisol, thyroid stimulating hormone and prolactin in peripartum women with major depression', *Arch Womens Ment Health*, 2(12), pp. 149–161.

WHO (2015) *Maternal mental health*, *World Health Organization*. Available at: https://www.who.int/mental_health/maternal-child/maternal_mental_health/en/ (Accessed: 30 July 2020).

Zielinski, G. *et al.* (2013) 'Dietary fiber methods in Codex Alimentarius: Current status and ongoing discussions', *Cereal Foods World*, 58(3), pp. 148–152.