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The Relationship Between Biomarkers of Environmental Enteric Dysfunction with Vulvovaginal Candidiasis In Pregnant Mothers and Pregnancy Outcome (Stunting): A Literature Review

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Abstract

Birth outcomes, including premature births and stunting, have long-term health implications. The relationship between adverse birth outcomes and asymptomatic chronic gastrointestinal inflammation (environmental enteric dysfunction - EED) has not been well-understood. EED is a subclinical inflammation of the small intestine characterized by changes in intestinal morphology, decreased absorption capacity, and impaired barrier function. Stunting is defined as a long (LAZ) / high-for-age score z > 2 elementary school under the WHO Child Growth Standards media, which remains a form of global malnutrition, affecting ~155 million children <5 years. There are about 20% of stunting originating from the uterus which is largely driven by intrauterine growth restriction, premature birth, or both. The purpose of this systematic review is to provide an overview of the measurement of EED biomarkers in pregnant women with vulvovaginal candidiasis and pregnancy outcomes in stunting prevention. **Method**: This study uses a literature review design. Articles collected through Cochrane, Science Direct, Pubmed, Elseiver, Proquest (link obtained from unhas.ac.id library) Pubmed, WHO, Google Cendekia. The keywords used are environmental enteric dysfunction (EED), vulvovaginal candidiasis, pregnant women, intestinal permeability, intestinal biomarkers, L: M test. **Results and Discussion**: Based on the results of reviewing articles, EED biomarkers of pregnant women, specifically the L: M ratio and anti-flagellin serum and anti-LPS Igs concentrations measured at gestations ~18 weeks, are associated with adverse birth outcomes, especially shorter pregnancy periods and reduced baby length at birth. To our knowledge, this is one of the first studies to measure EED biomarkers in a sample of pregnant women and the first to examine the relationship between EED biomarkers and pregnancy outcomes (stunting). **Conclusion:** The concentrations of anti-flagellin and anti-LPS of the mothers measured at ~18 weeks of pregnancy were significantly associated with shorter pregnancies and reduction in infant length and LAZ at birth in samples of pregnant women and their newborns. These results provide preliminary evidence that maternal EED may be associated with pregnancy outcomes (stunting).

Keywords: environmental enteric dysfunction (EED), vulvovaginal candidiasis, pregnant women, intestinal permeability, intestinal biomarkers, L: M. Test

Introduction

The first 1000 days period of children which is often referred to as the window of opportunities is a golden period of rapid growth and development that does not occur in other age

groups[1]. The first 1000 day movement consists of specific nutrition interventions and sensitive nutrition interventions[2], [3]. According to the Guidelines for the Acceleration of the First 1000 Days of Life Movement, the specific nutritional interventions for pregnant women are in the form of iron and folate supplementation, supplementary feeding for pregnant women lacking chronic energy, prevention of helminth infections, distribution of insecticide-treated nets, and medication for pregnant women with malaria[4]. Micronutrients function as a stimulus for red blood cell formation, bone development, and brain development. Deficiency of one of these micronutrients can be a risk factor for anemia. One factor that must be considered by pregnant women is sanitation and household water treatment because the lack of concern to both can lead to the birth of a stunted child. Pregnant women need supports in coping with helminth infections and everything related to the digestive system needed in the absorption of nutrients from mother to fetus to avoid malnutrition in children. Prenatal and postnatal nutritional deficits and enteric and systemic infections clearly contribute to the occurrence of malnutrition, but recent findings involve a central role for environmental enteric dysfunction (EED), general disruption of small intestine structure and its function by blunting or intestine villus atrophy and inflammatory cell infiltration[5], [6].

Prenatal and postnatal nutritional deficits and enteric and systemic infections clearly contribute to the occurrence of malnutrition, but recent findings involve a central role for environmental enteric dysfunction (EED), general disruption of small intestine structure and function found in high prevalence in children living in unhealthy conditions[7]. Mechanisms that contribute to the failure of EED growth include intestinal leakage and high permeability, intestinal inflammation, bacterial dysbiosis and translocation, systemic inflammation, and nutritional malabsorption. Since EED has many causes and effects, it requires various approaches to adress[8,9].

The human gastrointestinal system is the home of most microbes including intestinal microbiota. The human intestine has about 100 trillion microbiota cells consisting of 1,000 different species[10]. The human immune system plays an important role in maintaining homeostasis with microbiota to ensure that the mutual relations with the host can be maintained[11]. Microbiome in the gastrointestinal tract of a newborn baby is similar with adult microbiome during the first year of life. As human gets older, the microbiome changes since it is influenced by breast milk, fever, familiarization of complementary foods, and the use of antibiotics[12].

Environmental enteric dysfunction (EED) is a subclinical inflammation of the small intestine characterized by changes in intestinal morphology, decreased absorption capacity, and impaired barrier function[13]. This condition is likely to develop from chronic exposure to enteropathogens as a result of living in an environment contaminated with poor water, sanitation and hygiene conditions. EED is a global health problem that needs to be concerned, especially considering its high prevalence and showing the relationship with poor growth outcomes in children living in low and middle income countries[14].

The prevalence of short toddlers in Indonesia tends to be static. The results of Basic Health Research in 2007 showed that the prevalence of short toddlers in Indonesia was 36.8%. In 2010, there was a slight decline to 35.6%. However, it increased again in 2013 to 37.2% and based on the data from Nutrition Status Monitoring in 2015, the prevalence of short toddlers in Indonesia was 29%. It finally reached 30.8% in 2018[15], This value has decreased to 27.5% in 2016. However, it again increased to 29.6% in 2017 and the decrease in stunting rates in Indonesia only reached 4% between 1992 and 2013[16]. One of the factors of stunting can be caused by a yeast infection in the vagina toward the vulva (vulvovaginalis candidiasis) during pregnancy.

Vulvovaginal candidiasis is affected by the cycle and concentration of hormones in a woman's body. Most sufferers are between menarche and menopause, especially those who are pregnant. There are approximately 1/3 pregnant women in the third trimester have candida in their vagina. The physical environment allows and makes it easier for people to be infected or more at risk from causes of the disease. The main factor causing vaginal candidiasis is a matter of cleanliness. Fungal infections can be caused by dirty water used to clean the vagina[17].

Based on research conducted by Jacqueline M Lauer (2018) in Uganda, biomarkers of enteric dysfunction in the environment of pregnant women are associated with the birth of premature and stunting children in Uganda. However, research on the relationship of EED biomarkers with vulvovaginal candidiasis in pregnant women and pregnancy outcomes (stunting) has not been found. Thus, there needs to be a study that specifically examines the relationship of biomarkers from environmental enteric dysfunction in pregnant women with vulvovaginal candidiasis in stunting prevention.

Method

The author conducted a literature review from December 2018-September 2019 from English and Indonesian literature. The sources obtained from the free Journal namely; Cochrane, Science Direct, Pubmed, Elseiver, Proquest (the link obtained from Unhas.ac.id library) Pubmed, WHO, CDC, Google Scholar and several other websites that provide articles related to the author's research plan. There are also several free journal articles in PDF format, such as: Plus One, Vaccine, Nutrients, Scientific Reports, Microbial Ecology in Health & Disease, Cell Press, Nature Reviews/Gastroenterology & Hepatology, Arch Dis Child, Mycopathologia, Nature Immunology, FEMS Micobiology Reviews, FEMS Microbiology Reviews, International Journal of Molecular Sciences, Nature Communications, F1000 Research, Infection and Drug Resistance, European Journal of Clinical Microbiology and Infections Disease, Seminar in Fetal and Neonatal Medicine, Antibodies, Trends in Immunology, J Vet Res, Frontiers, in Veterinary Science, International Journal of MS Care, Gastroenterology, British Journal of Nutrition, BMC Veterinary Research, Nutrition & Metabolism, Animal Production Science, Journal of Human Genetic, Future Microbiol, International Journal Of Emergency medicine, BMC gastroenterology, Frontiers in Pediatrics, Science of the Total Environment, Journal of Clinical Medicine, Human Pathology, Medical Hypotheses, Trends in Molecular Medicine, Nature Cell Biology, Am. J. Trop.Med.Hyg, The Journal of Nutrition, Int. J Clin. Pharm and other sources such as textbooks from libraries, UNICEF reports, WHO, Ministry of Health, thesis and Indonesian dissertation.

Reviewing the article used the PICOS principle (participants, interventions, comparisons, results, research designs), so the keyword used was EED as the first word; the second word was vulvovaginal candidiasis, the third word was pregnant women, the fourth word was intestinal permebility, the fifth word was intestinal biomarkers and the sixth word was the L: M test. The subjects were pregnant women with the result being changes in the length of the baby's body or the HAZ score. The literature review technique in this article did not synthesize the statistical results (meta-analysis), but the final conclusions obtained could be scientifically justified as an effort to overcome the problem of stunting.

Results

Based on the initial review of the incidence of candidiasis which is the cause of premature birth, premature rupture of membranes and low birth weight, it is necessary to scientifically review the literature with the following procedures:

1. Gather information from various sources:

a. Journal: Articles that were found related to the theme between 2009 - 2019. Access international journals through Cochrane Central Science Direct, Pubmed, Elseiver, Proquest (the link obtained from Unhas. ac.id library), WHO, CDC,Google Scholar and National journals between 2009 and 2019 used as references which are suitable with the theme. Access journals via (Google Scholar) by entering Keywords:

   1. EED: there were 1466 articles and 20 articles were taken
   2. Vulvovaginal candidiasis: there were 148 articles and 52 articles were taken
   3. Pregnant women: 235 there were 235 articles and 15 articles were taken
   4. Intestinal Permeability: there were 27,759 articles and 25 articles were taken
   5. Intestinal Biomarkers: there were 36,470 articles and 15 articles were taken
   6. LM Test: there were 253 articles and 10 articles were taken

b. Online Report (Basic Health Research) and access the web of the ministry of health; there are 5 articles found

c. Book : there are several theories quoted from the book, and the books used were 15 books from 1980 to 2010.

2. Gather the material that has been obtained into Mendeley's software.
3. Making research synthesis from journals and other materials that have been obtained.
4. Reviewing the material obtained to ensure the literature review conducted can improve the information on the research variables

Table 1. Results of Review of Articles Related to EED Biomarkers and Pregnancy Outcomes in the Incidence of Candidiasis In Pregnant Women

Author	Tittle	Design	Results
Lauer, et all, 2018 14	Biomarkers of maternal environmental enteric dysfunction are associated with shorter gestation and reduced length in newborn infants in Uganda	a prospective cohort study	Complete birth outcome data were recorded for 220 infants within 48 h of delivery. Mean ± SD gestational age was 39.7 ± 2.1 wk, and 7% were born preterm. Mean ± SD length and length-for-age z score (LAZ) at birth were 48.1 ± 3.2 cm and −0.44 ± 1.07, respectively. L:M ratio was not associated with any birth outcome. In adjusted models, higher concentrations of natural log-transformed anti-flagellin immunoglobin G (IgG) and anti-LPS IgG were significantly associated with shorter length of gestation (β:−0.89wk;95%CI:−1.77,−0.01wk,andβ:−1.01wk;95%CI: −1.87, −0.17 wk, respectively) and with reduced length (β: −0.80 cm; 95% CI: −1.55, −0.05 cm, and β: −0.79 cm; 95% CI: −1.54, −0.04 cm, respectively) and LAZ at birth (β −0.44 z score; 95% CI: −0.83, −0.05, and β: −0.40 z score; 95% CI: −0.79, −0.01.
Andrew J., 2015	Assessment of Environmental Enteric Dysfunction in the SHINE		EED is a virtually ubiquitous, but poorly defined, disorder of the small intestine of people living in conditions of poverty that begins early in infancy and persists. It may plausibly impact linear growth, neurodevelopment, oral vaccine responses, and immune ontogeny, and several

	Trial: Methods and Challenges		trials are under way to evaluate the impact of preventive or treatment approaches for EED. Several research groups are actively evaluating novel markers of EED, but currently there is no accepted case definition or gold-standard biomarker, making field studies challenging. The SHINE trial provides an opportunity to longitudinally explore disease mechanisms, using the most robust current and emerging biomarkers of EED to better understand the impact of public health interventions on the causal pathway to stunting
Jian-Jun Yang, 2011 18	Histidine Decarboxylase Is Identified as a Potential Biomarker of Intestinal Mucosal Injury in Patients with Acute Intestinal Obstruction	This prospective study	In the critical care setting, the development of IMI in patients with AIO is associated with a high mortality due to the lack of methods or biomarkers for diagnosis of IMI (55). Although several serum (such as D-lactate, α-GST, I-FABP and DAO) and urine biomarkers (such as I-FABP and TXB2) have been used for diagnosing IMI in patients with AIO, all of them lack sensitivity as well as specificity, and thus their diagnostic values in clinical practice are limited. Therefore, the identification of novel biomarkers of IMI with higher specificity and sensitivity for diagnosis, prognosis and treatment has potential benefits for improving the clinical strategy and outcome of IMI in patients with AIO, and a useful and unique serum or urine biomarker of IMI is urgently needed
Najeeha T. Iqbal et al, 2019 19	Pathobiome driven gut inflammation in Pakistani children with Environmental Enteric Dysfunction	Subjects included in this analysis were part of a prospective community-based active surveillance birth cohort and were followed longitudinally for anthropometrics and biomarker measurements	In the context of EED, the present study highlights the association between enteropathogens and linear growth–an association hypothesized to be mediated through enteric and systemic inflammatory pathway. The key findings of our study are: a) the presence of at least one enteropathogen in fecal samples at 6 and 9 months of age (Table 1) (at least one bacteria, one protozoa and one virus); b) a negative correlation of delta LAZ with observed pathogen at 6 months (Table 2); and c) an association of specific enteropathogens with positive or negative changes in beta estimates of EED biomarkers as outcome variable. Overall we found that subclinical infection with entropathogen was marginally associated with linear growth. The presence of similar pathogens such as Giardia, Campylobacter and Cryptosporidium also showed substantial negative association in MAL-ED cohort
Najeeha T. Iqbal et al, 2018 20	Promising Biomarkers of Environmental Enteric	A Prospective Cohort study	we found that both systemic inflammation and EED are associated with linear growth, likely through IGF-1. While gut specific biomarkers, GLP-2 and MPO are weak drivers of systemic inflammation, they correlate strongly with

	Dysfunction: A Prospective Cohort study in Pakistani Children		IGF-1, which in turn correlates strongly with linear growth. While we are unable to say that GLP-2 and MPO are exclusive correlates of EED, we would like to propose that based on our current study data, these biomarkers should be included in the panel of tests that define EED in future studies that focus on prevention and treatment of this disorder

Based on the results of the literature review from the research of Lauer et al, 2018, biomarker tools used for dichotomous birth outcomes, including stillbirth, premature birth, LBW, stunting, and wasting, found that a significantly higher L: M ratio (0.16 ± 0.26 than 0.08 ± 0.12, P <0,05, P <0,05) and anti-flagelin IgA concentration (1.93 ± 0.75 than 1.58 ± 0.67, P <0,05) caused the preterm babies (n = 15) than the term babies. In addition, we found significantly higher% LE mothers (0.92 ± 1.16 than 0.49 ± 0.71, P <0.05) and lower anti-flagelin IgG (0.99 ± 0.35 than 1,16 ± 0.29, P <0.05) for wasted babies (n = 13) than those who are not. Overall, we observed a simple negative correlation between the L: M ratio and biomarkers serum, with a significant association observed between the ln L: M ratio and ln anti-LPS IgA and anti -LPS IgG (r = −0.15 and − 0.19, respectively P <0,05 for both).

Discussion

A prospective cohort study in pregnant women in Mukono, Uganda by Lauer et al. using hypothesis testing that maternal EED biomarkers, specifically the L: M ratio and serum anti-flagellin and anti-LPS Ig concentrations measured at gestational age ∼18 weeks are associated with outcomes pregnancy: stunting, low birth weight and premature rupture of membranes. Based on the literature review, this is one of the first studies to measure EED biomarkers with samples of pregnant women and the first to examine the relationship between EED biomarkers and pregnancy outcomes (stunting, bblr and premature rupture of membranes). Lauer et al found that mothers who had higher anti-flagelin and anti-LPS IgG, but not in IgA, the concentrations were significantly associated with pregnancy outcomes, including shorter gestational age and reduced infant length at birth and LAZ adjusted linear regression model. Since it was not associated with birth weight, the mothers with anti-flagellin and anti-LPS IgG were also significantly associated with higher WLZ infants at birth. In other words, an increase in maternal anti-flagellin and anti-LPS IgG is associated with shorter and heavier infants. We did not find this or any relationship between mothers with L: M ratios or in % LE and interesting primary or secondary birth outcomes. In addition, the study also found a simple negative correlation between serum biomarker concentrations and L: M ratios which is in line with the results of several recent studies: in 539 young Bangladeshi children aged 18 months, Campbell et al., in 375 Brazilian children aged 6 to 26 months where low to moderate yield was found among EED biomarker panels. Guerrant et al. found an equally weak correlation among 18 proposed EED biomarkers, including between anti-flagellin and anti LPS Igs and L: M ratio.

One of the plausible explanations for this difference was that the L: M test, specifically % LE, reflected the intestinal permeability while the anti-flagellin and anti-LPS concentrations captured the immune / inflammatory response to increased bacterial translocation. However, it should be noted that the results of our study differ from the results of research conducted by Campbell et al. which reported a significant association between plasma concentrations of both endotoxin and immunoglobulin (Ig) G-endotoxin nuclei antibodies (EndoCAb) and increased lactulose recovery (r = 0.36, P <0.02 and r = 0.35, P <0.005, respectively) as well as between the plasma concentrations of both endotoxin and EndoCAb and poor growth (r = −0.30, P <0.02 and r = .60,64, P <0,0001,

respectively) in Gambian infants. So far, the increased concentrations of anti-flagellin and anti-LPS have been observed in some cases of other chronic enteric conditions such as SBS and IBS. Ziegler et al. compared serum from the patients who depend on parenteral nutrition with SBS (n = 23) with non-SBS control subjects (n = 48 healthy adults and n = 37 adults who needed parenteral nutrition during critical illness) and found flagellin, LPS, or both in 61% of SBS patients compared with 0% in control subjects. The patients with SBS experienced significant increases in anti-flagellin Ig, including IgA, IgG, and IgM, than the control subjects (P < 0.001). Likewise, Dlugosz et al., compared serum from patients with 3 different IBS subtypes (total n = 88) with healthy control subjects (n = 106) and found a significant increase in LPS concentrations in patients with IBS dominant diarrhea than the control subjects. (P = 0.0155). They found an increase in the concentration of antibodies against flagelin in all patients with IBS than the control subjects (P = 0.0018). In a limited number of studies, an increase in anti-flagellin and anti-LPS concentrations has also been associated with poor growth results. Especially in 590 Tanzanian children, Mc Donald et al. found that infants at 6 weeks who fell in the highest quartile of anti-flagelin IgA, anti-LPS IgA, antiflagellin IgG, and anti-LPS IgG concentration were 2.02 (95% CI: 1.11, 3.67), 1.84 (95% CI: 1.03, 3.27), 1.94 (95% CI: 1.04, 3.62), and 2.31 (95% CI: 1.25, 4.27) times, respectively, were more likely to be thin under 18 months of follow-up care than children with the lowest concentration of Ig in the quartile (trend-P <0.05)

Although the pathway by which maternal EED contributes to adverse birth outcomes is not well established, Lauer et al. hypothesize that intestinal barrier dysfunction results in systemic exposure to flagellin and LPS, which in turn stimulates the adaptive immune / inflammatory response. Although the resulting immune / inflammatory response might contribute to an important line of defense against bacterial infection, such response can also contribute to the pathogenesis of EEDs and ultimately result in poor child growth and adverse birth outcomes in cases of maternal EED and pregnancy. This hypothesis is supported by several studies that have previously shown an association between general inflammatory maternal biomarkers and adverse birth outcomes, especially proinflammatory cytokines and C-reactive protein. In a prospective cohort study of Tanzanian mothers who were HIV-positive (n = 44) and HIV-negative (n = 70), Wilkinson et al. found that systemic inflammation, measured by a 9-plex maternal plasma cytokine panel, was associated with poorer anthropometry. In this study, higher maternal plasma TNF-α concentrations were associated with prior labor (.71.7 weeks, P = 0.039) and lower birth weight (−287 g, P = 0.020), and higher umbilical cord TNF- α (−1.43 cm, P = 0.036) and IL12p70 (−2.4cm, P = 0.008) were associated with a reduction in infant length (42). Furthermore, in a study with a Filipino mother and her baby (n = 327), Kuzawa et al. (43) found that systemic inflammation, measured by maternal C-reactive protein during pregnancy, was associated with infant weight loss (.00,047 ± 0.017 kg · log-mg-1 · L-1), long (−0.259 ± 0.092 cm · Log-mg-1 · L-1), and number of skin folds (−0.520 ± 0.190 mm · log-mg-1 · L-1) (all P <0.05).

Conclusion

The concentrations of anti-flagellin and anti-LPS of the mothers measured at ∼18 weeks of pregnancy were significantly associated with shorter pregnancies and reduction in infant length and LAZ at birth in samples of pregnant women and their newborns. These results provide preliminary evidence that maternal EED may be associated with pregnancy outcomes (stunting).

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