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Low zinc serum affects insulin-like growth factor-1 level in dehydrated pregnant women

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ABSTRACT

Maternal body fluids imbalance affects amniotic fluid, serum sodium-potassium, edema, and preeclampsia. Insulin-like growth factor-1 (IGF-1) is a growth hormone and a regulator in sodium balance regulation. This study aimed to determine the correlation of IGF-1, zinc, calcium, and sodium with hydration status and the nutrients impact to IGF-1 based on hydration status of pregnant women at Kebon Jeruk Health-Center, West Jakarta. This cohort-prospective study was conducted in December 2016 to January 2018. A total of 66 pregnant women in the second trimester were examined. Urine color, urine specific gravity, serum sodium, serum osmolality and urine were used as hydration status indicators. Zn, Ca, Na, and IGF-1 levels as the growth indicator from mother to fetus. Pearson correlation test, independent t-test and linear regression were used in statistical analysis. There were no differences in IGF-1, Zn, Ca, and Na serum between the two groups ($p \geq 0.05$). There was no relationship between Ca, Na and IGF-1 level ($p \geq 0.05$). The regression results show a positive relation that low zinc serum affect IGF-1 level in dehydrated pregnant women. Therefore, it is necessary for pregnant women to consume zinc-rich foods to increase IGF-1 level and keep hydration status with water consume 3.0 L per-day.

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1. INTRODUCTION

Insulin-like growth factor-1 (IGF-1) is one of the important factors in evaluating the deficiency and excess growth hormone in adults and modulating growth in the fetus as a placental regulator which influences nutrient transport (glucose, protein, and fatty acids) in placenta [1]–[4]. The IGF system consists of two growth factors, two receptors and seven insulin-like growth factor binding proteins (IGFBP). This system operates by anabolism and cell proliferation [5].

Fetal growth is influenced by placental growth hormone (PGH), which is a specific hormone in pregnancy that plays a role in trophoblastic invasion, fetal growth, and maternal adaptation. This is due to somatotropic, lactogenic and lipolytic properties which are like the pituitary growth hormone (GH), although growth activity is seen more in other functions [6]. Growth factors can be synthesized by specific cells that have large variations in body tissue. For example, the IGF hormone substance from human liver and fibrous can be found in cell divisions of bones, muscles, and other tissues. IGF synthesis can be stimulated by growth hormones, from the pituitary gland which optimally influences growth [7]–[9].

About 70-80% of pregnant women experience nausea and vomiting due to hormonal changes, especially in the first trimester of pregnancy [10]. Excess vomiting can lead to weight loss of up to 5% from before pregnancy, dehydration, electrolyte imbalance, ketosis, and the need for hospitalization in the hospital [11]. Dehydration is the process of a condition that occurs in a person when the body fluid loss is greater than the intake [12].

As one of the regulators, IGF-1 plays a role in regulating sodium balance by increasing the transport of basal transepithelial sodium and aldosterone which are stimulated in distal aldosterone nephrons (ASDN) [13] Insulin and IGF-1 can bind each other receptors with low affinity 50-100 times to their cognitive receptors, it is unclear which specific part of the receptors mediated the respective sodium transport responses in ASDN [14]. Not only sodium, but zinc minerals also that play a role in the metabolic activity of more than 200 enzymes which have a function in growth and development may be related to growth hormone [15]. Other studies found a positive relationship between circulating IGF-1 levels, serum IGFBP3, and serum calcium [16]. The body fluid and electrolyte balance are the result of a mechanism that is sensitive to changes in water and electrolytes in the body [17]. The role of endocrine and metabolic factors in fetal growth can be seen in late pregnancy, which depends on the maternal environment that occurs during the period of conception [18], [19]. Body fluid imbalance may affect pregnancy such as the imbalance of amniotic fluid, imbalance of serum sodium and potassium so that it disrupts oxygen pump to the heart, edema in pregnant women, and preeclampsia. This will impact the pregnancy output [20], [21].

In previous studies, pregnant women with serum zinc levels below 72-333 μg/L resulted in a pregnancy output of low birth weight (LBW) compared to mothers who had normal serum zinc levels [22], [23]. Thus, zinc status can to some extent explain the abnormalities that occur in pregnant women. Based on the exposure, not many studies have looked at the correlation of IGF-1 levels as a growth indicator, zinc, calcium, and sodium with pregnancy hydration status. This allows for an association with hydration status that can affect serum zinc levels, serum calcium, serum sodium, and IGF-1. As is known, hydration specifically plays a role in transporting nutrients in the form of carbohydrates, vitamins, minerals, and other important nutrients into and out of cells as well as removing metabolic waste products [24], [25]. Therefore, it is necessary to study the role of IGF-1 in macro and micro minerals in the case of pregnancy hydration which aims to determine the correlation of IGF-1 levels, zinc, calcium, and sodium with hydration status and the nutrients impact to IGF-1 levels based on hydration status of pregnant women in Kebon Jeruk Health Center, West Jakarta.

2. METHOD

2.1. Design, place, and time

This study is a cohort-prospective study, which aims to study the interaction of serum levels of IGF-1, zinc, calcium, sodium, and hydration status. This study was conducted in seven area community health centers in Kebon Jeruk sub-district, West Jakarta, starting from December 2016 to January 2018. The study site was chosen with the criteria of being in a densely populated area, low to middle socio-economic conditions, and the highest number of pregnancy services. This study has received ethical approval from the Health Research Ethics Commission in the Faculty of Medicine, University of Indonesia, Jakarta with a number: No.869/UN2.F1/ETHICS/2016 dated October 10, 2016.

Subjects were second-trimester pregnant women (16-18 weeks' gestation) who met the inclusion criteria: i) doing pregnancy examination at a health center in the study site; ii) being in the second trimester of pregnancy (>12-24 weeks); iii) healthy (e.g., no secondary infections), based on the results of a health examination; iv) have no history of babies with low-birth-weight or stunting (<48 cm); v) the aged between >18 and 35 years; vi) the height between 150-165 cm; vii) body mass index (BMI) (18.5-25.0); viii) have had a history of urinary tract infections; ix) have had a history of diarrhea, nausea, or vomiting in early pregnancy; x) having plan to deliver in a health center; xi) fill out the informed consent; xii) comply with research procedures; and xiii) never had a caesarean delivery, since there is a possibility of a cesarean delivery in the next pregnancy, meanwhile, this research focuses on subjects with middle to lower socio-economic levels and there's no facility caesarean in the health center. The total subjects who are willing to follow this study are 66 pregnant women in the second trimester. The reason behind this is that sampling pregnant women >12 weeks or the second trimester is a cycle of hormonal changes and a phase of rapid fetal growth. With the sampling proportion the minimum total sampling as 64 subjects for two groups. The explanation in Figure 1.

2.2. Data collecting

This study looked at hydration status on 32-37 weeks of gestation by taking blood and urine at 6 points; 3 points on 32-34 weeks of gestation and 3 points on 35-37 weeks of gestation. The observation was continued until the parturition (birth process) to draw blood in the umbilical vein (umbilical cord) as an indicator of IGF-1 biomarkers.

Data on characteristics of pregnant women, medical history, and anthropometry such as maternal age, body weight during pregnancy, blood pressure, pulse, thyroid gland, leg edema, eye conjunctiva, eye sclera, and fetal movements over five months were obtained from subject interviews conducted by trained enumerators for 15-20 minutes at week 16-18 of gestation. The screening was done with midwives and doctors through repeated measurements, checking cohort book and KIA book (maternal and child health). Urine color, urine specific gravity, serum sodium, urine, and serum osmolality are measured from 6 observation points to see the mother's hydration status, then micro and macro minerals (Zn, Ca, Na) levels, and IGF-1 levels as indicators of growth from mother to fetus. Biomarker's measurement of hydration status and macro-micro minerals taken through sample of blood (20 ml) and urine (50 ml) are carried out by a trained phlebotomy and the sample examination is carried out to an accredited laboratory. Urine specific gravity was tested by urinometer method, urine and plasma osmolality were checked by osmometer, urine color was checked by the check your own urine (PURI) indicator, and serum sodium was examined by Ion selective electrode (ISE) method. Dehydrated group was defined by osmolality ≥500 mOsm/kg, serum osmolality >299 mOsm/kg, urine specific gravity >1.015, and urine color score >4.0. Biomarkers measuring Zn, Ca, and Na serum levels are taken through veins in the 3rd trimester, which is 34-37 weeks of gestation. Serum Zn levels were measured using the inductively couple plasma-mass spectrophotometer (ICP-MS) method and serum Ca levels were measured through the Arsenazo III Dye method. IGF-1 levels are taken through umbilical veins (umbilical cord) shortly after birth (parturition) and measured by the enzyme-linked immunosorbent assay (ELISA) method.

This study used blood (20 ml) and urine (50 ml) as a sample. The blood taken from intravenous blood. Urine taken from spot urine at 14.01-16.00 local time. All of the examination of hydration biomarkers was carried out in an accredited laboratory collaborating with this study [26].

Equipment used in the study were Camry digital scales, Combur 10 M (Roche), Osmomat 3000 Gonotec GmBH, PURI Indicator, ADVIA 1800 (for sodium examination) with ADVIA chemistry ise buffer (siemens) reagents, ICP-MS Agilent 7700x, and Architect C-8000. The questionnaire of characteristics of the subject, medical history, and anthropometry were adopted from the Basic Health Research (RISKESDAS) 2013 questionnaire.

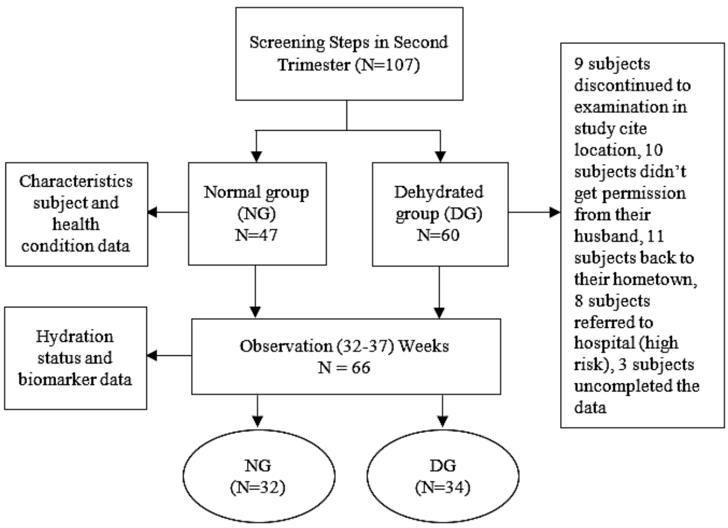

Figure 1. Flowchart sampling

2.3. Data analysis

Data is processed and analyzed with Microsoft Office Excel and SPSS 20.0 programs. The data collected was analyzed descriptively and presented in the form of mean, median, and standard deviation (SD). Hydration category is obtained based on 5 biomarkers from the 6 points where: if more than or 2 of the indicators has value above the normal baseline, it will be included in the dehydrated group and vice versa. Generally, biomarkers used in pregnancy hydration status are urine color, urine osmolality, and urine specific gravity [27]–[30]. Based on previous study, we used 2 indicators as the cut-off value hydration status. IGF-1 biomarker data, serum zinc levels, serum calcium and serum sodium levels are presented with mean and standard deviations value (numerical data). The bivariate analysis test used an independent t-test to see differences in subject characteristics, IGF-1 levels, macro and micro minerals, and Pearson correlation to see the relationship of macro and micro mineral interactions with hydration status. Data were analyzed at 95% confidence interval (CI) and a significance level $p<0.05$.

3. RESULTS AND DISCUSSION

3.1. Characteristics distribution of subject based on hydration status

Hydration status is measured based on an average of 5 biomarkers from the 6 points of data collection: urine color, urine specific gravity, serum sodium, urine, and serum osmolality. This study divided the subjects into two groups based on hydration status namely dehydration (51.5%) and normal (48.5%). Based on these data it was found that there were no differences in subject characteristics over five months between the two groups ($p\geq 0.05$).

Physiological regulation of sodium and water intake and output was needed to maintain balance. The regulation of body fluid and sodium balance affects blood pressure, were excess sodium in blood causes hypertension. The behavioral and neuroendocrine mechanisms that regulate fluid and salt balance are interdependent, with kidney output being offset by changes in thirst and at a lower level, appetite. This is maintained in the third trimester of pregnancy [20], [21]. Other studies mention that pregnant women over 35 years are at high risk of giving birth to children with Down syndrome, miscarriage, high blood pressure and pregnancy complications [31], [32].

Based on the data as shown in Table 1, it was found that there were no differences in subject characteristics; maternal age, gestational weight gain, blood pressure, pulse, thyroid gland, leg edema, eye conjunctiva, eye sclera and fetal movements over five months between the two groups ($p\geq 0.05$). In this study blood pressure and pulse were in the normal range. Leg edema, eye conjunctiva, eye sclera and fetal movements between the two groups are in normal condition. These symptoms are one of the things that describe the body fluids balance of sodium and potassium. BMI before pregnancy in the two groups there are differences ($p<0.05$) and are in the normal category (18.5-24.0 kg). Normal gestational weight gain was ranged from 11.5-16.0 kg [33]. Gestational weight gain is associated with a high risk of pregnancy problems such as high blood pressure, low birth weight, and miscarriage [33].

Table 1. Characteristics distribution of subject based on hydration status

Variable	Dehydration (n=34)	Normal (n=32)	p-value
Age (year)	25.5±4.7	26.8±4.9	0.28
BMI (kg/m^2)	23.8±3.5	21.4±3.6	0.00
Gestational weight gain (kg)	12.4±4.2	11.5±3.8	0.34
Blood Pressure:			
Systole (mmHg)	108±10	108±7	0.86
Diastole (mmHg)	67±6	69±6	0.32
Pulse (minute)	87.8±18.6	90.3±18.3	0.58
Thyroid gland:			0.18
Not palpable (0)	34 (100.0)	29 (90.6)	
Palpable but not visible (Ia)	0 (0.0)	2 (6.3)	
Visible in normal position (II)	0 (0.0)	1 (3.1)	
Leg edema:			
Not present	34 (100.0)	32 (100.0)	
Eye conjunctiva:			1.000
Present	1 (2.9)	0 (0.0)	
Not present	33 (97.1)	32 (100.0)	
Eye sclera:			0.97
Present	0 (0.0)	1 (3.1)	
Not present	24 (100.0)	31 (96.9)	
Fetal movements above five months:			
Not present	34 (100.0)	32 (100.0)	

The data are normally distributed in the form of mean±SD, SD: standard deviation, Independent *t*-test. Categorical data are presented in the form of n (%), Chi-square test

3.2. IGF-1, Zn, Ca, and Na levels and hydration status

Zn, Ca and Na serum levels were measured in the third trimester of pregnancy and the average value was calculated. While IGF-1 levels are taken in the venous umbilical shortly after the mother gives birth. Table 2 shows no differences in IGF-1, Zn, Ca, and Na serum levels with hydration status between the two groups ($p\geq 0.05$).

Table 2. Differences of IGF-1, Zn, Ca, and Na levels with hydration status

Variable	Dehydration (n=34)	Normal (n=32)	p-value
IGF-1 level (ng/ml)	44.4±10.8	46.9±13.3	0.40
Zn level (µg/dl)	45.19±5.96	43.45±3.86	0.16
Ca level (mg/dl)	8.7±0.3	8.8±0.2	0.94
Na level (mEq/L)	137.5±1.0	137.7±1.2	0.31

Data presented in form of mean±SD; SD: standard deviation, independent *t*-test.

This study shows that the levels of Ca and Na in the Dehydration and normal groups are at normal values. It is possible that in the third trimester of pregnancy, the mother can adapt and get Ca supplements for pregnant women from the Community Health Center which is one of the government programs. Na levels in the two groups were at normal levels (135-153 mEq/L).

3.3. Correlation of Zn, Ca, and Na and IGF-1 levels

Table 3 showed that there is no relationship between the serum level of Ca, Na, and IGF-1 ($p \geq 0.05$). Although there was a positive correlation between the serum level of Zn and IGF-1 (0<0.1) (r=0.21). To determine the interaction of these nutrients on hydration status, a regression test was carried out on IGF-1. The results show there is a tendency for a positive correlation between Zn and IGF-1 levels, then Zn and hydration status control of IGF-1 are shown in Table 4. A relationship of Zn with IGF-1 levels were found ($p<0.05$).

Table 3. Correlation of Zn, Ca, and Na and IGF-1 levels

Variable	IGF-1 level (ng/ml)	
	r	p-value
Zn level (µg/dl)	0.21	0.07*
Ca level (mg/dl)	-0.11	0.37
Na level (mEq/L)	-0.18	0.12

Correlation test, p<0.1

Table 4. Regression model of Zn level and hydration status to IGF-1

Variable	β	(SE)β	95% CI	p-value
Constant	11.82	-	(-19.76-43.40)	0.45
Zn level[*)]	0.72	0.30	(0.02-1.41)	0.04
Hydration status	26.07	1.08	(-31.44-83.59)	0.36
Interaction of Zn level and hydration status	-0.51	-0.93	(-1.81-0.78)	0.43

Linear regression test, [*]p<0.05. Hydration status: (1) normal, (0) dehydration

Increased Zn level of pregnant woman with dehydration can increase the IGF-1 level. Increased Zn per 1 mg in dehydrated mothers will increase 0.72 IGF-1 levels. In normal mothers, an increase of 1 mg Zn increases IGF-1 levels by 26.28. Thus, in people who are dehydrated, high consumption of Zn can help increase IGF-1 levels. During normal pregnancy, the digestive tract and it is supporting organs changed, that it causes excessive nausea and vomiting (hyperemesis gravidarum) in the early trimester of pregnancy. About 0.8-3.2% of pregnant women, resulting weight loss, dehydration, and malnutrition [34], [35].

While Zn levels between the two groups were below normal values (70-250 µg/dl). It is possible that at the beginning of the trimester the mother experiences excessive nausea and vomiting but cannot catch up with the intake of zinc in the third trimester. This study did not measure Zn serum levels in the first trimester. Therefore, we didn't predict weather the Zn serum levels is low or not in that period. Zn is a micro mineral that has a role in fetal growth and development. Zn deficiency can cause stunted fetal growth, miscarriage, and premature [14], [36].

Zinc concentration in serum affects T3, T4 and serum TSH levels. Zinc transporters (ZnTs) are present in the hypothalamus, pituitary, and thyroid, although their function is unknown [37]. In addition, other research states that the use of zinc and Se supplements in combination with a low-calorie diet can affect resting metabolism, timed up-and-go test performance, and selenium levels in overweight people [38]. Thus increasing levels of zinc and selenium intake may be beneficial in preventing the new onset of hypothyroidism in overweight adult women [39], [40].

IGF-1 is two peptide hormones that share structural homology, which acts as an important regulator in fetal growth and development [41]. In addition, IGF-1 and IGFBP3 play a role in the development of autoimmune beta cells [42]. More than 70.0% IGF-1 is found in all body tissues and synthesized in the liver under the regulation of growth hormone (GH), thus serum IGF-1 represented the endogenous secretion of growth hormone (GH). Serum IGF-1 is influenced by age, body mass index, and geographical area [42].

Several studies found the relationship of serum Zn and IGF-1 and IGFBP3 serum respectively. This assumes that there was stimulating effect of Zn levels mediated by changes in IGF-1 levels and is closely related to growth hormone (GH) [43], [44]. Growth hormone is produced by the anterior pituitary gland, which have functions as the main regulator of formation and growth. This hormone also promotes linear growth by stimulating the division of prechondrocytes in the epophyseal plate. Therefore, it is used as a marker of the growth hormone GH-IGF1-insulin-like growth factor-1 that divides growth status, growth potential, and response to preventive and therapeutic interventions [44]. IGF-1 levels, unlike GH, are more stable in healthy individuals. This is proven by IGF1 directly stimulating growth without depending on GH stimulation. Infact, studies on mice show that interventions for growth failure due to lack of Zn levels are caused not only by low IGF-1 levels, but by inhibiting the anabolic IGF-1 action [14]. Other studies have found that oral administration of Zn supplements effectively increases Zn status for children lacking zinc, IGF-1 and IGFBP3 secretory levels, GH potentiality, and height [45]. Thus, zinc levels in pregnant women influence high levels of IGF-1.

4. CONCLUSION

This study found there were no differences in subject characteristics; maternal age, weight gain during pregnancy, blood pressure, pulse, thyroid gland, leg edema, eye conjunctiva, eye sclera, and fetal movements over five months between the two groups. No differences in IGF-1, Zn, Ca, and Na serum levels with hydration status between the two groups. There is no relationship between Zn, Ca, Na serum levels with IGF-1. However, there is a positive correlation between Zn and IGF-1 levels.

It is recommended to consume zinc-rich food sources in both groups of dehydrated and normal pregnant women to increase IGF-1 levels. It should be noted that this research is only limited to pregnant women from lower middle-income and the sample is limited. Therefore, more samples and heterogeneous socio-economic clustering are needed. On the other hand, this study is needed to see the effectiveness of zinc administration in pregnant women to increase IGF-1, especially in cases of pregnancy hydration.

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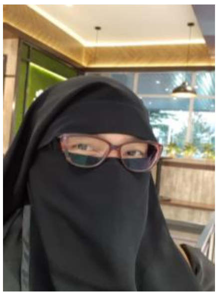

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