

Associations of Maternal Serum Zonulin and Elements Concentrations with Neonatal Birth Weight: A Case-Control Study

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ABSTRACT

Introduction: Intake of micronutrients and zonulin levels (as a marker for intestinal permeability) during pregnancy can be effective on birth weight of infants. However, no studies have investigated the relationship between the infants birth weight and maternal zonulin level.

Aim: This study aimed to compare the zonulin levels and maternal trace elements in infants with low birth weight (LBW) and Normal Birth Weight (NBW) and its relationship with weight, length and head circumference of infants.

Materials and Methods: In this study, 368 infants were divided into two groups: case (n=82) with birth weight of <2500 gm and control (n=286) with birth weight of ≥2500 gm. Maternal zonulin, zinc, calcium, copper and iron levels were evaluated. Weight, length and head circumference of infants were measured. The maternal serum level zonulin and micronutrients between the two groups were assessed using Student t-test or Chi-squared

test and the relationship between variables using Spearman's rank correlation.

Results: A significant difference was seen in the maternal zonulin and zinc serum levels between the LBW and the NBW infants (<0.001). No significant difference was observed in the calcium, copper, and iron levels between the two groups. A significant positive relationship was seen between maternal serum zonulin and zinc concentration with the birth weight of the LBW infants (respectively $r=0.45$ and $r=0.41$) ($p<0.05$). No relationship was seen between maternal serum zonulin and zinc concentration with the length and head circumference of the infants.

Conclusion: The results showed that the maternal serum Zn level is associated with the infants birth weight. In addition, intestinal permeability, as a new factor could affect the birth weight and birth rate of the LBW infants. Further studies in this area are recommended.

Keywords: Nutrient deficiency, Low birth, Trace elements

INTRODUCTION

The nutritional needs increase during pregnancy. For the proper growth of the foetus, adequate intake of micronutrients is important during pregnancy [1-3]. However, the evidence shows that micronutrient intake during pregnancy is suboptimal [4]. Nutrient deficiency during pregnancy may cause an increase in the birth rate of the LBW infants.

Zinc, iron, calcium and copper, are among the necessary micronutrients during pregnancy. Zinc is essential for embryonic development [5]. The Recommended Dietary Allowance (RDA) for zinc is increased during pregnancy from the 8mg/day to 11 mg/day [6]. Zinc affects the growth of the embryo and foetus by cell proliferation and protein synthesis [7,8]. Zinc deficiency in the first trimester of pregnancy can affect the developing foetus [9]. While studies, have suggested that there is a direct association between maternal zinc level during pregnancy with the birth weight of the infants, conflicting results have also been reported [10,11]. In many studies, zinc supplementation was not able to prevent the birth of the LBW or Small For Gestational Age (SGA) infants [12,13]. Need for iron during pregnancy increases due to the decreased concentration of red blood cells. It was suggested that the incidence of low birth weight infant was significantly more in mothers who were anaemic in their third trimester [14]. Calcium plays a vital role in bone formation [15]. The urinary absorption and excretion of calcium increases during pregnancy [16]. An intake of more calcium during pregnancy can reduce the chances of low-weight infant birth [17].

In addition to the micronutrient intake also weight gain during pregnancy are of the factors affecting weight of infant birth [18]. Meta-analysis and systematic review studies show that the increased amount of weight gained during pregnancy can reduce the risk of the LBW infant birth [19,20]. Recently, it has been suggested that intestinal permeability is considered an important factor in obesity and weight gain, an increase in intestinal permeability and absorption leads to development of obesity [21]. Zonulin plays a role in intestinal permeability by adjusting the amount of intracellular tight junctions in the digestive tract [22].

Circulating levels of zonulin are considered as a good marker for assessing intestinal permeability [23]. Despite the possibility of the relationship between serum levels of maternal zonulin and infant birth weight, no research studies have examined the association between these two. Thus, because of the importance of elements in foetal development and a possible association between maternal zonulin level with outcome of pregnancy, this study was designed and conducted in order to investigate the relationship between levels of trace elements and maternal zonulin level with weight, length and head circumference of infants.

MATERIALS AND METHODS

Study Population

This case-control study was conducted on 368 mother-infant pairs in the Gynaecology unit, Sina referral Hospital Hospital of Ahvaz Jundishapur University of Medical science in Ahvaz, Khozestan,

Iran, during June 2015 and January 2016. According to the inclusion and exclusion criteria of the study, 368 mother-infant pairs (infants; 186 boys, 182 girls) were selected from 534 mother-infant pairs. The sample size was based on a similar study on the relationship between maternal and neonatal serum trace element concentrations with neonatal birth weight [24].

Women attending prenatal care after 28 weeks of pregnancy, at the maternity clinic. Inclusion criteria included mothers at the age of 20-40 years, healthy mothers, without a history of underlying disease and consent to giving blood samples. Mothers were excluded if they smoked, or if they were with gestational diabetes, preeclampsia, twin and multiple pregnancies or babies with birth defects, drug or alcohol abuse.

For biochemical assessment on maternal serum, fasting blood (5 ml) was collected. Samples were used to measure levels of zonulin, calcium, iron, copper and zinc. Other biochemical tests were evaluated at the hospital lab. Serum zonulin levels were measured by ELISA. Systolic and diastolic blood pressure of mothers was measured using a barometer. During the first 24 hours after birth in the obstetrics clinics, the anthropometric status of newborns was measured. Weight (with an accuracy of 0.1 kg), length and head circumference of infants (with an accuracy of 0.1 cm) was measured using a fabric meter. Based on low birth weight, infants were divided into two groups. The case group was defined as infants with a weight less than 2500 gm (and >1000gm), and the control group was defined as infants with similar or a weight more than 2500 grams. An informed consent form was gained from subjects. The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences. (Act No. IR.AJUMS.REC.1394.517).

| Variable | LBW (n=82) | NBW (n=286) | p-value* |
|---|--------------|--------------|----------|
| Infants | | | |
| Boys/Girls | 21/61 | 165/121 | <0.001 |
| Weight (gr) | 2062.5±511.2 | 3308.3±527.1 | <0.001 |
| Length (cm) | 44.8±6.9 | 52.1±3.7 | <0.001 |
| HC (cm) | 30.4±3.5 | 34.3±4.4 | <0.001 |
| Mother | | | |
| Age (yr) | 26.1±5.9 | 27.1±5.4 | 0.11 |
| Cesarian (%) | 47 | 44 | 0.57 |
| Haemoglobin (gr/dl) | 11.38±2.8 | 11.63±1.15 | 0.07 |
| Haematocrit (%) | 36.13±2.8 | 36.30±3.96 | 0.72 |
| RBC (10 ⁶ /mm ³) | 4.33±0.37 | 4.47±0.61 | 0.08 |
| MCV | 83.75±4.13 | 82.37±8.59 | 0.15 |
| MCH (pg) | 26.31±1.5 | 26.61±4.5 | 0.55 |
| MCHC (%) | 31.46±0.6 | 31.83±1.1 | 0.06 |
| RDW-CV (%) | 14.1±1.9 | 14.1±1.1 | 0.75 |
| RDW-SD (fL) | 43.43±5.1 | 42.56±3.3 | 0.07 |
| WBC (Number/mm ³) | 11.1±3.1 | 10.9±3.1 | 0.72 |
| Platelets (10 ⁹ /mL) | 216.4±38.2 | 207.8±55.7 | 0.18 |
| MPV (fL) | 8.5±0.9 | 9.2±5.8 | 0.28 |
| PDW | 15.5±0.3 | 15.6±0.3 | 0.06 |
| Systolic BP (mm-Hg) | 11.4±1.1 | 11.3±0.8 | 0.15 |
| Diastolic BP (mm-Hg) | 7.4±0.7 | 7.2±0.7 | 0.11 |
| Lymphocyte (10 ⁹ /mL) | 2.2±0.6 | 2.4±2.2 | 0.36 |
| Granulocyte (10 ⁹ /mL) | 8.2±2.9 | 8.3±2.7 | 0.82 |
| MIC | 1.5±1.1 | 1.6±1.2 | 0.57 |

[Table/Fig-1]: Baseline characteristics of LBW and NBW infants. LBW: Low Birth Weight, NBW: Normal Birth Weight, NS: Non-Significant; HC: Head Circumference; RBC: Red Blood Cell; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Haemoglobin; MCHC: Mean Corpuscular Haemoglobin Concentration; WBC: White Blood Cells; MPV: Mean Platelet Value; PDW: Platelet Distribution Width; BP: Blood Pressure; MIC: Minimum Inhibitory Concentration; *p-values are derived using t-test or chi-squared analysis.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL). Normal distribution of quantitative data was measured by the Kolmogorov-Smirnov test. Due to the lack of normal distribution of the data, nonparametric tests were employed. To compare differences between the groups, the Student t-test or Chi-square test were used.

The Spearman rank correlation was used to determine the relationship between Zonulin and Zinc levels and weight, Length and Head circumference in infants. Data was expressed as mean±SD. The level of significance was considered as p<0.05.

RESULTS

Of the 368 infants, 82 infants (22%) with a weight less than 2500 gm were assigned in the case group and 286 infants (78%) with a weight more than 2500 gm were assigned to the control group. The average weight of the newborns in the case group was 2062.5±511.2 and 3308.3±527.1 in the control group, respectively. A significant difference was observed between gender, body length and head circumference of infants among the case and control groups (p<0.001). The average age of mothers in the case (26.1±5.9) and the control (27.1±5.4) groups, was not significantly different. In addition, the mode of delivery, haematological parameters, systolic and diastolic blood pressure in the mother showed no significant difference between the two groups [Table/Fig-1].

| Variable | LBW (n=82) | NBW (n=286) | p-value |
|-----------------|------------|-------------|---------|
| Zonulin (ng/ml) | 7.4±1.3 | 9.2±1.6 | <0.001 |
| Ca (mg/dl) | 8.8±1.4 | 8.9±1.2 | 0.64 |
| Cu (ug/dl) | 206.1±38.6 | 215.6±24.3 | 0.06 |
| Fe (ug/dl) | 48.9±23.5 | 53.7±31.2 | 0.19 |
| Zn (ug/dl) | 64.4±8.2 | 78.2±9.1 | <0.001 |

[Table/Fig-2]: Comparison of serum Zonulin, Ca, Cu, Fe and Zn concentrations in mothers before delivery between LBW and NBW infants. LBW: Low birth weight, NBW: Normal birth weight. *p-values are derived using t-test or chi-squared analysis. Ca- Calcium, Cu-Copper, Fe-Iron, Zn-Zinc.

A significant difference was observed in maternal serum zonulin concentration between case and control groups (7.4±1.3 ng/ml vs 9.2±1.6 ng/ml). (p<0.001); however, no significant differences were observed in the concentration of calcium, copper and serum iron between the two groups of infants. A comparison between the zinc serum concentrations of mothers in the case (64.4±8.2) and control (78.2±9.1) groups showed a significant difference (p<0.001) [Table/Fig-2].

A significant correlation was observed between zonulin concentration (r=0.45) and maternal serum zinc (r=0.41) with the birth weight of infants in the case group (p<0.05); however, no significant correlation was seen between maternal serum zonulin and zinc concentration with the length of the body and head circumference in infants in the case group [Table/Fig-3].

| Variable | Birth weight | | Length | | Head circumference | |
|----------|-------------------|---------|--------|---------|--------------------|---------|
| | r | p-value | r | p-value | r | p-value |
| Zonulin | 0.45 ^a | <0.05 | 0.17 | NS | 0.11 | NS |
| Zn | 0.41 ^a | <0.05 | 0.15 | NS | 0.02 | NS |

[Table/Fig-3]: Association between Zonulin and Zn maternal concentrations with birth weight, length and head circumference in case group. NS: Non-significant; HC: Head circumference; *p-value is for spearman correlation, p<0.05 is statistically significant.

DISCUSSION

The study showed a significant relationship between maternal serum zonulin and zinc concentration with the birth weight of newborns with a weight less than 2500 gm, and maternal serum zonulin and

zinc serum levels in infants with a weight more than 2500 gm is significantly higher than LBW infants. However, this significant relationship was not observed between the maternal calcium, copper and iron serum levels. This is the first study that examined the relationship between intestinal permeability (zonulin; as a new marker) during pregnancy with body composition in infants.

The present study observed no association between maternal iron levels with anthropometric status in infants. In contrast, Alwan et al., reported that first trimester maternal Fe depletion is associated with higher risk of SGA. However, their study showed no evidence of association between maternal Fe depletion and preterm birth [24]. A systematic review and meta-analysis reported that anaemia in the first and third trimester was associated with the increased risk of LBW [25]. However, the results of some studies were consistent with our study [26,27]. The difference in results may be due to assessment of the iron level at different trimesters of pregnancy and characteristics of the population studied.

Our study suggested that there was no association between maternal calcium with anthropometric status in infants. Our results, are not consistent with other studies. Elizabeth KE et al., reported that Preterm and term LBW infants are born with significantly lower Calcium reserves at birth compared to term control infants [28]. Also, Durrani AM and Rani A suggested a significant correlation between the calcium intake of the mothers and the weight of newborn in all trimesters of pregnancy [29]. Khoushabi F et al., suggested that maternal serum calcium concentration influenced the birth weight of neonates [30].

In the present study, there was no significant correlation between maternal copper and LBW. In contrast, Wasowicz W et al., reported Cu concentration in preterm infants is significantly higher than in full-term infants [31]. Ghebremeskel K et al., suggested a negative correlation between cord blood copper and anthropometric status (birth weight and head circumference) in newborns [32]. Also, Sikorski R et al., reported a negative correlation between neonatal birth weight and maternal copper level [33].

Tsuzuki S et al., examined the association of serum trace elements of mothers and infants with birth weight. Their results showed that serum selenium concentrations in mothers and premature infants are significantly lower than mothers and term infants. However, no relationship was reported between serum concentrations of copper, iron and zinc in mothers and infants with birth weight [27]. Studies about the relationship between the birth weight and maternal serum zinc concentrations show conflicting results. The results of the study conducted by Wang H et al., consistent with the results of our study showed that the zinc serum levels in mothers are positively associated with birth weight [34]. The study conducted by Abass RM et al., in Sudan, showed that maternal zinc and copper levels in LBW infants are less than babies with normal weight [35]. Also, a clinical trial showed that the intervention of zinc during pregnancy can cause improvement in the weight and head circumference of babies [36]. In contrast with our results, Khadam N et al., reported that maternal zinc concentration is more in premature than full term deliveries [37].

Zonulin as a mediator for the permeability of the intestinal tract can affect body weight through changes in modulating intracellular tight junctions [38]. Zonulin is associated with the gut microflora. Recent findings show that the amount and composition of gut microflora are different between obese and lean individuals [39]. A study conducted by Moreno-Navarrete JM et al, showed that serum zonulin levels are correlated with Waist To Hip Ratio (WHR), BMI and fasting glucose [40]. On the other hand, zonulin levels are associated with energy intake and intake of food components. Increased energy intake and consumption of high-fat diet increases the zonulin levels of plasma. Also, increase in fiber intake prevents weight gain by reducing the serum zonulin levels [41]. A study conducted by Zak-Goląb A et al., showed that serum zonulin level in obese individuals is significantly

more than the normal weight people. In addition, the serum zonulin level is related to the body fat percentage, BMI and energy intake, and it is inversely related to protein intake [42].

This study is the first study that has examined the relationship between intestinal permeability during pregnancy with body composition in infants. In this study, we used a new marker (zonulin) to evaluate the intestinal permeability which is one of the strengths of this study.

LIMITATION

In this study, the mother's blood samples were used to evaluate the relationship between maternal biochemical factors with anthropometric status in infants. However, the maternal serum is not a significant tool to show the umbilical cord blood status.

CONCLUSION

Overall, the results show that maternal serum zonulin and zinc levels are associated with birth weight in infants. In order to, give birth to a healthy baby, adequate and balanced healthy nutrition during pregnancy is recommended.

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